ABSTRACT During the past decade, use of complementary and alternative medicine (CAM) by the American public increased from 34% in 1990 to 42% in 1995 with related out-of-pocket expenditures estimated at $27 billion. Among cancer patients, use of CAM ranges between 30 and 75% worldwide and includes dietary approaches, herbs and other biologically based treatments such as melatonin, shark cartilage and high dose vitamins and minerals. Concerns about herb-nutrient-drug interactions and product quality and standardization emphasize the need for rigorous research. In 1998, Congress mandated the creation of the National Center for Complementary and Alternative Medicine (NCCAM) to conduct and support such research of CAM therapies. The NCCAM portfolio for oncology is rapidly growing. As of July 2001, 26 projects are underway, two specialized centers are funded for cancer research and four botanical centers are cofunded with the Office of Dietary Supplements. Investigations are targeting herbs and complex herbal formulas; single dietary supplements and complex dietary regimens; biological agents; and mind-body, body-based and frontier approaches. Of these, biopharmacologic and herbal therapies are a major focus of research. The NCCAM portfolio illustrates how research of CAM, particularly studies of biopharmacologic and herbal approaches for cancer, is developing systematically and rigorously. J. Nutr. 131: 3037S–3040S, 2001.

KEY WORDS:  • alternative • complementary • cancer • research • NCCAM
ethnic groups in San Francisco (3), 49.6% among breast cancer survivors in Canada (5), 34% of prostate cancer patients in a Veteran's Administration population (7) and 41% (high dose vitamins) among prostate patients undergoing radiation therapy (8). Often, antioxidants are used in combination with conventional oncology treatment.

Recent surveys of cancer patients indicate that disclosure of CAM use to physicians is low (9). The possible effect of heritability and dietary supplements on the efficacy of conventional treatment, amelioration of side effects or toxicity of conventional treatment, recurrence and survival are as yet unevaluated by compelling, well-controlled studies in preclinical models or cancer patients. As in conventional medicine, the level of evidence for safety and efficacy of CAM ranges from anecdotal reports to encouraging data from small, phase I and II clinical trials to data from larger, randomized clinical trials. The high use of CAM and low disclosure of use to the health care team signal the need for improved monitoring by oncologists if they are to respond appropriately to any atypical clinical responses of these patients (Fig. 1). Rigorous scientific testing of CAM therapies, however, is of vital importance to inform medical advice and establish clinical practice guidelines for CAM use.

**Mandate to NCCAM**

The goal of NCCAM is to support the accumulation of evidence on CAM by supporting preclinical, clinical and mechanism-of-action studies. Opportunities for research are prioritized using several criteria, i.e., prevalence of use, potential for public effect, feasibility, cost and the opportunity to expand the science base. The strategy is to support investigator-initiated research, thereby allowing the scientific community to identify priority areas of research. Projects with the greatest scientific merit, potential for success and possible long-term benefit to the American public are awarded in a two-level NIH peer-review process.

The extramural division of NCCAM is charged with increasing the number of NCCAM-supported grants and co-funding CAM-related activities at other NIH institutes and centers. The oncology portfolio at NCCAM is evolving with increasing numbers of meritorious and fundable research applications from the oncology community. As of July 2001, NCCAM was funding 26 research projects in oncology and several trials cosponsored by other NIH institutes. Most of these studies are evaluating biopharmacologic and herbal therapies and almost half are clinical research. The clinical research includes phase I, II and definitive phase III multicenter trials of widely used agents with various endpoints, i.e., survival, disease-free survival, neuroendocrine markers, psychosocial and physical functioning and quality of life.

**NCCAM research of biopharmacologic and herbal therapies**

NCCAM is cofunding, with the Office of Dietary Supplements, four botanical centers in the United States. The centers are charged with the following tasks: identifying and characterizing botanicals, assessing bioavailability and activity, exploring mechanisms of action, conducting preclinical and clinical evaluations, providing training and career development and advising NCCAM in the selection of products for testing in randomized clinical trials. The four centers are engaged in research on wide ranging topics: polyphenols from soy, grapes and tea (Purdue University); herbal supplements for women's health (University of Illinois); botanicals in Ayurveda from the Indian subcontinent (University of Arizona); and supplements with green tea, soy, St. John's wort and yeast-fermented rice (University of California-Los Angeles).

To expand the infrastructure for conducting innovative CAM research in oncology, NCCAM also funds specialized research centers at Johns Hopkins University and the University of Pennsylvania. These specialized research centers conduct basic and clinical studies to assess the efficacy, safety and mechanisms of action for CAM therapies for cancer. The Specialized Center of Research in Hyperbaric Oxygen Therapy at the University of Pennsylvania is testing the effect of an emerging specialty of medicine, oxygen at greater than atmospheric pressures, on head and neck cancer as well as tumor growth and metastasis. The Johns Hopkins Center for Cancer Complementary Medicine is engaged in studies of natural supplements and herbal mixtures. Researchers at Johns Hopkins are testing the antioxidant effects of herbs in cancer cells, antioxidant and anti-inflammatory properties of soy and tart cherry on pain with established animal models and the safety and efficacy of a popular mixture of Chinese herbal medications (PC-SPES) in men with prostate cancer.

The NCCAM oncology portfolio also includes a growing...
number of investigator-initiated research to evaluate pharmacologic agents and herbal medicines. These projects cover the research continuum from preclinical, mechanism-of-action studies to definitive, randomized placebo-controlled trials. The studies and the institutional sites by type of study are listed in Table 1.

**Upcoming funding for new initiatives**

**CAM research programs at the comprehensive cancer centers.** NCCAM has agreed to cofund with the National Cancer Institute supplements to five comprehensive cancer centers for CAM research programs. These programs will conduct basic, clinical (prevention, therapeutic and palliative), epidemiologic, population science and cancer control CAM research, including pilot and phase I and II clinical trials. The supplements are expected to be awarded in the fall 2001.

**Drug-herb interactions.** Funds will be awarded to meritorious applicants in fall 2001 for investigator-initiated research (i.e., preclinical and phase I and II clinical studies) to study adverse botanical-drug interactions during therapy or anesthesia, establish possible synergistic combinations of botanicals with pharmaceutical drugs and increase our knowledge of the mechanisms of action of botanicals.

**TABLE 1**

**Studies evaluating pharmacologic agents and herbal medicines**

<table>
<thead>
<tr>
<th>Preclinical</th>
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<tbody>
<tr>
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<tr>
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**Phase I**

| Morinda citrifolia (Noni): maximum tolerated dose and toxicity, bioavailability and pharmacokinetics, and antitumor and symptom control. (University of Hawaii) |   |

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**Phase I**

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**Phase II**

- Soy isoflavones: effect on prostate-specific antigen, sex hormone binding globulin, endogenous sex hormones and isoflavone levels; surrogate markers for osteoporosis; quality of life in men with prostate cancer (n = 60); and peri- and postmenopausal women with or without hormone replacement therapy (n = 120). (Stanford University)

**Phase III**

- Shark cartilage: effect on survival (overall, progression free, metastasis free) and tolerability in newly diagnosed patients (n = 756) with IIIa-b, unresectable nonsmall cell lung cancer in combination with chemotherapy and radiotherapy (MD Anderson Comprehensive Clinical Oncology Program)
- Shark cartilage: effect on survival, quality of life, tolerability for patients (n = 600) with advanced breast and colon cancer (Mayo North Center Cancer Treatment Group)
- Gonzalez nutritional regimen: effect on survival and quality of life for patients (n = 72-90) with stage II-IV pancreatic cancer. (Patients self-select to the nutrition or gemcitabine treatment.)

**CAM therapies at the end-of-life for cancer and human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS).** Funds will be awarded to meritorious applicants in fall 2001 for phase I and II clinical studies of CAM therapies that expand the therapeutic and palliative care options beyond technological and conventional pharmacologic approaches.

**Integration of CAM.** Funds will be awarded to meritorious applicants in fall 2001 for health services research that investigates the barriers and facilitators to integration of effective CAM with conventional health care practices; determines whether efficacy studies of CAM (research under ideal conditions) can be translated to effectiveness (real-world settings) in integrated models and evaluates planned or ongoing CAM programs (e.g., outcomes or cost-effectiveness).

**Antioxidants and concurrent chemotherapy and radiotherapy.** A workshop is being planned for 2002 to identify the major gaps in our knowledge about use, justification and safety of antioxidants with conventional chemotherapy and radiotherapy.

In conclusion, the NCCAM oncology portfolio is growing, and additional grants will be awarded in fiscal year 2002 in response to several new initiatives as well as investigator-initiated applications. NCCAM funded research and current initiatives as well as an archive of past funding opportunities are available on the website (15). One primary focus of the current oncology portfolio is biological and herbal agents. Given the widespread use of these CAM approaches by cancer patients and the possibility that their biologic activity may interfere or enhance conventional cancer treatment, such studies are critical. Although some of these agents will show no promise and subsequently will be discarded, others should prove to be beneficial and, it is hoped, be incorporated into interdisciplinary medical treatment. An investment into the research of these therapies is critical if we are to separate the wheat from the chaff and inform patients and the medical community (16). Information on CAM therapies for cancer is currently available in a searchable database of CAM on PUBMED (17), summaries of CAM cancer therapies are available on the Physician's Database Query (18), fact sheets are available at the NIH Clinical Center website (19) and protocols of ongoing clinical research are available online (20).

With continued support from the public, increased funding to maintain the current momentum and participation of the oncology research community and CAM providers, the efficacy and safety of many CAM biological and herbal therapies as well as mechanism for activity will be established.

**LITERATURE CITED**