VIII.
National Cancer Institute

INTRODUCTION

The National Cancer Institute (NCI), in cooperation with extramural institutions and the John E. Fogarty International Center for Advanced Study in the Health Sciences (FIC), of the National Institutes of Health (NIH), supports international health research through bilateral agreements, grants, and contracts. The Institute supports about 3,000 intramural research scientists and staff, some 1,000 Visiting Scientists and Exchange Scientists, and about 8,000 extramural grants, contracts, and training awards. The work of outstanding scientists is supported through fellowships, cooperative projects, exchanges of personnel and materials, and workshops. In recent years, NCI has obligated approximately $50 million for foreign grants and contracts, the NIH Visiting Program, bilateral scientist exchanges, workshops, and international dissemination of cancer information.

NCI's international effort, coordinated by the Office of International Affairs (OIA) in the Office of the NCI Director, works in conjunction with programs at other NIH Institutes and FIC. Advances in cancer research result from NCI support and from support by other U.S. and foreign government agencies, industries, private nonprofit institutes, and individual philanthropists. Individual scientists initiate most of the cooperation in cancer research here and abroad, and other institutions also support international activities directly, without NCI involvement. NCI does take the initiative, however, when it is expedient to exploit a scientific opportunity. The research divisions within NCI are the Division of Basic Sciences, the Division of Clinical Sciences, the Division of Cancer Biology, the Division of Cancer Epidemiology and Genetics, the Division of Cancer Prevention, the Division of Cancer Control and Population Sciences, and the Division of Cancer Treatment and Diagnosis.

International Workshops

One way in which OIA fosters joint research between U.S. and foreign scientists is by cosponsoring international workshops. The OIA workshops program brings together small groups of U.S. and foreign scientists who are at the forefront of their fields of research, to discuss their newest research that has not yet been published.

The U.S.-Japan Cooperative Cancer Research Program is a joint program of NCI and the Japan Society for the Promotion of Science. The program sponsored a 2-day U.S.-Japan Cancer Symposium, in Bethesda, Maryland, on February 22–23, 2000. The program also sponsored smaller workshops on the following topics:

- Molecular Basis of Tumor Invasion and Metastasis: Strategic Application to Cancer Therapy (Maui, Hawaii);
- Carcinogenesis by Chronic Infection and Inflammation (Nara, Japan); and
- Molecular Pathogenesis of Phacomatosis (Boston, Massachusetts).

Other workshops cosponsored by OIA included the following:

- Biological Therapy of Cancer (Munich, Germany);
- 25th Asia Pacific Cancer Conference (Madras, India);
- 2nd International Conference on Tumor Microenvironment (Eilat, Israel);
- New Frontiers in Prostate Cancer (Haifa, Israel);
- Role of Radiotherapy in the Management of Cancer (Haifa, Israel);
- Joint Palestinian-Israeli Conference on Colon Cancer (Ramalla, Israel [West Bank]);
- 5th Course in Cancer Genetics and Pediatric Oncology (Sestri Levante, Italy);
- 2nd International Symposium on PET (positron emission tomography) Applications in Oncology (Madrid, Spain);
- Molecular Approaches to Cancer Diagnosis, Prognosis, and Treatment (Salamanca, Spain); and
- International Cancer Symposium (Hanoi, Vietnam).

NCI was a cosponsor of the 11th World Conference on Tobacco or Health, in Chicago, Illinois, in August 2000. This conference is the preeminent international gathering of tobacco researchers and public health practitioners; more than 5,000 participants from 173 countries attended, including 300 from low- and middle-income nations.

TABLE VIII-1.

NCI Office of International Affairs: Scientist Exchange Programs, Fiscal Year 2000

Country or Area	Visits	Months
Argentina	2	12.5
Armenia	1	2.0
Australia	2	7.0
Belarus	1	2.5
Bolivia	1	10.0
Bulgaria	1	12.0
Chile	1	0.3
China	16	88.2
Costa Rica	1	0.5
Egypt	6	19.3
Finland	1	0.5
France	1	0.5
Gabon	1	6.0
Germany	3	12.3
Greece	4	11.8
Haiti	1	1.0
Hungary	3	6.0
India	5	26.0
Israel	6	44.0
Italy	2	6.5
Japan	5	30.0
Jordan	4	18.0
Kenya	1	2.0
Korea	5	22.5
Mexico	1	1.5
New Guinea	1	0.5
Pakistan	1	0.5
Palestine	3	16.0
Philippines	1	0.5
Poland	2	4.0
Russia	10	48.5
Slovakia	1	0.3
Spain	2	12.3
Turkey	6	37.0
Ukraine	3	14.5
Venezuela	1	7.5
Vietnam	3	6.0
Total	**109**	**490.5**

TABLE VIII-2.

Foreign Scientists at NCI Under NIH Visiting Program, Fiscal Year 2000

Country or Area	Scientists
Algeria	3
Argentina	7
Australia	11
Austria	4
Belarus	1
Belgium	4
Brazil	2
Bulgaria	2
Burkina Faso	1
Cambodia	1
Canada	40
Chile	2
China	135
Colombia	2
Croatia	3
Cyprus	1
Czech Republic	5
Denmark	5
Egypt	5
Estonia	1
Fiji	1
France	29
Germany	53
Greece	7
Hong Kong	1
Hungary	12
India	54
Iran	3
Israel	11
Italy	39
Jamaica	1
Japan	138
Kazakhstan	1
Korea	81
Latvia	1
Lebanon	3
Macedonia	1
Malaysia	2
Mexico	7
Mongolia	1
The Netherlands	15
New Zealand	1
Norway	3
Pakistan	2
Peru	3
Philippines	1
Poland	13
Portugal	2
Romania	2
Russia	47
Senegal	1
Serbia	1
Singapore	2
Slovakia	4
South Africa	3
Spain	27
Sweden	3
Switzerland	4
Thailand	1
Ukraine	2
United Kingdom	17
Venezuela	1
Taiwan	17
Total	**853**

Scientist Exchange and Other Training Programs

The Scientist Exchange Programs bring U.S. and foreign scientists together for either short-term (less than 1 year) or long-term cooperation. Long-term exchanges are supported by NCI and the European Organization for Research and Treatment of Cancer (EORTC); NCI and the Japanese Foundation for Cancer Research; and the Oncology Research Faculty Development Program.

The Oncology Research Faculty Development Program, sponsored by OIA, is a long-term program for young but established scientists from cancer research laboratories in developing countries. The program is designed to prepare these scientists for independent careers as investigators and for leadership positions in cancer research in their country. Foreign cancer research institutes nominate a limited number of scientists to the OIA selection committee. Each year, up to 16 candidates are accepted in NCI-supported laboratories. The cost is shared by NCI and the sponsoring laboratory.

During FY 00, OIA shared the costs of supporting 109 Exchange Scientists from 37 countries, for a total of 490.5 person-months, through the short- and long-term exchange programs. The distribution of these scientist exchanges for FY 00 is shown in Table VIII-1.

In addition to the Exchange Scientists supported by OIA, 853 foreign scientists visited NCI laboratories under the NIH Visiting Program (Table VIII-2). NCI also contributed to the funding of more than 100 short-term International Cancer Technology Transfer Fellowships, a program administered by the International Union Against Cancer (UICC).

Each year, individuals from a number of foreign countries participate in the Cancer Prevention and Control Academic Course, offered by the Division of Cancer Prevention. In FY 00, participants included representatives from Armenia, Egypt, Hungary, Kenya, Korea, the Palestinian Authority, and Vietnam.

Cancer Registration in Developing Countries

Population-based cancer registries collect information on all cases of cancer in a defined geographic area, to estimate cancer incidence rates in the general population by variables such as gender, age, cancer site, and stage of disease. The establishment of cancer registries is a critical first step in public health planning, assessment of facility and manpower needs, research, and establishment of effective cancer control programs.

OIA sponsored attendance of personnel from developing countries (a) at courses on cancer registration and genetic counseling, which were conducted by the International Agency for Research on Cancer (IARC), Lyon, France, and (b) at a course on cancer registration, at Emory University, Atlanta, Georgia. OIA also sponsored two courses on cancer pain control, in Santa Cruz, Bolivia, for participants from all over Latin America.

In cooperation with the Middle East Cancer Consortium, OIA has sponsored cancer registry training programs in Bethlehem, Israel (West Bank), and Amman, Jordan. Training programs have also been held in Santa Cruz, Bolivia; Shanghai and Beijing, China; and Trivandrum, India. The course in Bolivia was attended by participants from Argentina, Bolivia, Brazil, Colombia, Costa Rica, the Dominican Republic, Mexico, and Peru. OIA also sponsors participants from several developing countries for the annual meeting of the International Association of Cancer Registries. In addition, OIA is providing assistance to develop infrastructure at cancer registries in Nigeria, Swaziland, Yemen, and Zimbabwe.

Senior staff of the NCI's Surveillance, Epidemiology, and End Results (SEER) Program are part of an international team that has updated the *International Classification of Diseases for Oncology (ICD-O)*. NCI worked on the revisions with IARC, headquartered in Lyon, France. The *International Classification of Diseases for Oncology, 3rd edition (ICD-O-3)* was field tested in several areas of the world and will be implemented for cases diagnosed in North America beginning January 1, 2001. Documents prepared for *ICD-O-3* have been made available on the SEER web site and have been downloaded by researchers throughout the world. Training materials are available from the SEER training web site (http://www.training.seer.cancer.gov), and a videotaped satellite broadcast can be ordered from the SEER web site (http://www.seer.cancer.gov/Publications).

Cancer Information Dissemination

Electronic Access

International dissemination of information on cancer research and treatment is a high-priority activity for NCI. In 1990, OIA began information dissemination projects at cancer centers in developing countries, to provide access to the latest published cancer research literature and treatment information through the NCI databases CancerLit and PDQ (Physician Data Query). NCI provided free subscriptions to these two databases on compact disk for a limited time, and the host institute provided the necessary computer hardware. By 1994, more than 50 information dissemination sites were in operation worldwide. With increasing availability of the Internet to access these databases, the compact disk program was discontinued in 1995.

The increasing availability of electronic telecommunications networks, even in many countries with an otherwise poor communications infrastructure, is revolutionizing the means by which individuals can access biomedical research and treatment information. The MEDLINE database of the National Library of Medicine is freely available on the Internet, either on the Grateful Med system (http://igm.nlm.nih.gov) or via PubMed (http://www.ncbi.nlm.nih.gov/PubMed/). Most of the PDQ database is available in English and Spanish via the CancerNet web site (http://cancernet.nci.nih.gov). The entire CancerLit bibliographic database is available through the CancerNet web site. In a typical month in 2000, 220,000 user sessions were logged on this site, and about 10% of the users were from outside the United States and Canada.

PDQ information summaries on cancer prevention, screening, treatment, and supportive care can also be obtained from CancerFax, an automatic fax-back service, and CancerMail, an electronic mail (e-mail) service. The summaries on treatment and supportive care are available in Spanish, either directly from NCI or from the University of Chile, Santiago. In addition, these services offer monthly CancerLit searches on selected cancer topics. The NCI Liaison Office in Brussels, Belgium, collects information on clinical protocols from Europe for the PDQ database. PDQ is distributed by EORTC through EuroCODE, an electronic communication network for European oncologists.

For CancerFax, the telephone on a fax machine is used to call 1-301-402-5874, and recorded instructions are followed to retrieve documents. To access CancerMail, users send e-mail messages containing codes for desired documents to the NCI computer and receive the requested information in return. A contents list can be obtained by sending e-mail to cancermailicicc.nci.nih.gov with the word "help" as the message. CancerMail information also is available via the Internet on a number of gopher servers, web servers, and other secondary distribution sites.

Print and Audiovisual Materials

With the American Cancer Society and the Pan American Health Organization (PAHO), OIA cosponsored the production of a Spanish-language edition of the American Cancer Society *Textbook of Clinical Oncology,* which is being distributed free to many of the major medical libraries in Spanish-speaking countries and is being sold at a subsidized rate to medical practitioners there.

In collaboration with the American Health Foundation of New York and PAHO, OIA is cosponsoring the development of a Spanish edition of the elementary school (kindergarten through grade 6) health education program "Know Your Body," for use both in U.S. Latino schools and in foreign schools where Spanish is spoken. A translation into Polish is in process, and translations into other languages are planned. OIA previously supported an Israeli Health Education Scholar at the American Health Foundation, thus facilitating the introduction of a Hebrew and an Arabic version of "Know Your Body" into Israeli and Palestinian schools.

NCI has many collaborative research agreements with IARC. One agreement addresses the identification of agents and exposures that may pose a carcinogenic risk to humans. Monographs containing the results of risk evaluations are published by IARC as individual volumes.

NCI is providing memberships in its Information Associates Program to approximately 45 libraries in foreign cancer centers or medical schools in Africa; Asia, including the Near East; the Caribbean; Central and Eastern Europe; and Latin America. This Program, developed by the International Cancer Information Center, provides subscriptions to the Journal of the National Cancer Institute (JNCI) and JNCI Monographs; access to the PDQ database and to CancerLit digests of citations and abstracts via electronic bulletin board or Internet connection; and a variety of other cancer information services.

Distribution of a "Cancer Seminars" series on videotape is continuing. Copies of these lectures are available to libraries of 110 foreign cancer institutes, giving young foreign scientists the opportunity to access the latest findings in cancer research. Recent lectures include the following:

- Cell Life and Cell Death;
- Immune Response to Self and Mutated Human Cancer;
- Consequences and Mechanisms of Loss of TGF-β (tumor growth factor β) Responsiveness in Carcinogenesis;
- Gene Discovery in Breast Cancer;
- Etiology and Pathobiological Consequences of p53 Mutations in Human Cancer;
- Cancer Vaccines for Solid Tumors;
- Contemplating the Completion of the Human Genome Sequence;
- Transcriptional Coactivators in Virus Infection and Cancer;
- Cancer Drug Discovery: Rationalizing Empiricism;
- Use of Tumor Necrosis Factor in the Treatment of Cancer; and
- Creation of Human Cancer Cells.

Clinical Trials and Preclinical Drug Development

NCI facilitates international cooperation in clinical trials involving U.S. industry, which sometimes contributes pharmaceutical agents for such trials at no cost to the U.S. Government or foreign collaborating institutions. For example, clinical trials are being conducted in parallel in the United States and at the Russian (former All-Union) Cancer Research Center, Moscow, for the treatment of colon, colorectal, and breast cancers. Patients in these trials are receiving donated leucovorin or granulocyte colony-stimulating factor.

NCI Liaison Office

The NCI Liaison Office coordinates the Institute's research and treatment programs in Europe through a formal trilateral agreement with EORTC, the Cancer Research Campaign (CRC) of the United Kingdom, and a bilateral agreement with the Southern Europe

New Drug Organization. The Liaison Office is involved in the exchange of information, experimental drugs, and research protocols and in programs for international exchange of scientists. The Liaison Office collects, reviews, and submits European research protocols for inclusion in PDQ, which is distributed worldwide through various channels, including EORTC's EuroCODE. In addition, the Liaison Office participates on committees and in working groups involved in all aspects of cancer research and drug development throughout Europe. The Office also facilitates international exchange of experimental drugs for treating cancer, seeks new agents with therapeutic potential from European sources, and assists in the development of research protocols that ensure comparability between data gathered in Europe and in the United States. This comparability has resulted in recognition by the U.S. Food and Drug Administration of data from European drug trials. More recently, both CRC and EORTC obtained International Cooperative Project Assurance certificates from the Office for Human Research Protection, U.S. Department of Health and Human Services.

The EORTC-NCI Exchange Program, administered by the Liaison Office, offers support for up to 3 years for scientists from Europe or the United States to conduct research in an overseas facility. The NCI Liaison Office also supports short-term visits to the United States for European investigators involved in drug discovery and development. These exchange programs have fostered closer working relationships between European and U.S. investigators and have expedited development of several high-priority new compounds under study in Europe and the United States.

Cooperative Group Program

There is a long history of individual overseas institutions participating in the Clinical Trials Cooperative Group Program. Not all participating institutions receive financial assistance from NCI for this research; many investigators participate for the intellectual and emotional satisfaction of doing so, and their institutions subsidize the research. Participants involved in the Cooperative Group Program include the following:

- American College of Surgeons (Canada and Israel);
- Cancer and Leukemia Group B (Canada and England);
- Children's Cancer Group (Australia, Canada, and Switzerland);
- Eastern Cooperative Oncology Group (Canada, Israel, and South Africa);
- Gynecologic Oncology Group (Canada);
- •National Surgical Adjuvant Breast and Bowel Project (Australia, Canada, and New Zealand);
- North Central Cancer Treatment Group (Canada);
- Pediatric Oncology Group (Canada);
- Radiation Therapy Oncology Group (Canada); and
- Southwest Oncology Group (Canada).

The National Cancer Institute of Canada-Clinical Trials Group receives funding from the NCI Clinical Trials Cooperative Group Program under a cooperative agreement.

The EORTC Data Center, Brussels, Belgium, also receives funding from the Clinical Trials Cooperative Group Program, under a cooperative agreement. The purpose of the funding is to assist the center in efforts to standardize the structure of data management, data quality assurance, and auditing for European trials to correspond closely to U.S. standards and conventions. This effort to make data comparable permits use of EORTC data as well as U.S. data in assessment and interpretation of the efficacy of new cancer therapies. A number of joint U.S.-European treatment protocols focus on breast, ovarian, renal, bladder, and other cancers. Professional staff of the NCI Cancer Therapy Evaluation Program (CTEP) participate in the review and evaluation of proposed studies by EORTC's Protocol Review Committee, and senior staff members of EORTC and the Medical Research Council Clinical Trials Office in the United Kingdom serve as members of CTEP Concept Evaluation Panels for proposed U.S. phase III trials.

Some cancers or stages of disease have incidence rates or event rates so low that the NCI Cooperative Group and large European organizations such as EORTC cannot complete trials quickly unless they draw on the resources of many smaller national consortia. However, many of the smaller, nationally based groups do not have U.S. trial assurances, and because they are smaller and are generally staffed by volunteers, they may have neither the resources nor the inclination to apply for U.S. trial assurances. NCI is working with EORTC and other overseas agencies on possible solutions to this problem.

International Cooperative Biodiversity Group Program

International Cooperative Biodiversity Groups strive to achieve the interdisciplinary and synergistic goals of promoting biodiversity conservation, drug development, and economic growth. In addition to NCI, this initiative is cosponsored by the National Science Foundation; the U.S. Department of Agriculture; FIC; the National Institute of Allergy and Infectious Diseases; the National Heart, Lung, and Blood Institute; and the National Institute of Mental Health.

The International Cooperative Biodiversity Group Program supports broadly based, international, interdisciplinary projects to meet each sponsoring agency's missions and objectives in four general areas:

1. collaboration in drug discovery and development for diseases of concern to both developing and developed countries;
2. development of inventories of native species and indigenous knowledge;
3. training directed to the needs of an individual country; and
4. improvements in the scientific infrastructure of the host country.

Biomedical Imaging Program

NCI's Biomedical Imaging Program supports two cooperative agreements with international components. One study focuses on determining the usefulness of magnetic resonance imaging in diagnosing and characterizing breast cancer. This collaborative effort accrues data on patients from 14 clinical sites, two of which are located in Germany. The Program also funds the American College of Radiology Imaging Network, a cooperative group for clinical imaging studies. This group has begun its first multi-institutional trials and has had discussions with radiologists in Belgium, Germany, Italy, and the United Kingdom about joint European-North American clinical imaging trials. The second study, which involves two institutions in the United Kingdom and six in the United States, is designed to measure clinical tumor response to therapy by using magnetic resonance spectroscopy.

Cancer Therapy Evaluation Program

Working with the NIH Office for Protection From Research Risks, CTEP staff developed a model for International Cooperative Project Assurance (ICPA) that can be used by foreign groups to participate in the Cooperative Group research protocols. This model simplifies and speeds the collaborative process. In the past, if a foreign research group wanted to collaborate with a Cooperative Group, each institution in the group had to apply to the Office for Protection From Research Risks for assurance for each project. Under the ICPA procedure, an assurance application from a central body, such as a ministry of health, covers all institutions involved. Since the inception of ICPA, approvals have been given to the Australian Gastro-Intestinal Trials Group; the Australian-New Zealand Breast Cancer Trials Group; EORTC, Brussels, Belgium; the International Breast Cancer Study Group; the Italian Association of Pediatric Hematology and Oncology; the Peruvian Society of Medical Oncology; and CRC and the CRC Clinical Trials Unit, United Kingdom.

CTEP continues to provide investigational anticancer agents to overseas investigators involved in Cooperative Group activities and selected clinical trials, provided that the study procedures ensure protection of human subjects and compliance with local regulations. In addition to the Cooperative Group clinical trials, CRC is conducting two trials of bryostatin 1, one trial of 17-allylaminogeldanamycin (17-AAG), and one trial with suramin, all in the United Kingdom.

In response to the Request for Proposals for contracts for early clinical trials with emphasis on phase II studies, a team from the Princess Margaret Hospital, Toronto, Ontario, applied and competed successfully for one of the eight awarded contracts. With this award mechanism, CTEP will be supporting a variety of new phase II studies with Canadian investigators.

CTEP has increased international collaborative efforts in the development of cancer treatment with the National Cancer Institute of Canada and the European Drug Development Network, comprising EORTC, Brussels; the Southern Europe New Drug Organization, Italy; and CRC, United Kingdom. CTEP met with these groups at various international meetings to develop procedures for these joint research efforts and helped to facilitate the development or submission of a Drug Master File to the Food and Drug Administration, or both, for each of these groups.

Developmental Therapeutics Program

The Developmental Therapeutics Program (DTP) searches for drugs for the treatment of cancer and of acquired immunodeficiency syndrome (AIDS). Through the NCI Liaison Office, Brussels, more than 2,000 compounds per year come from European sources to DTP for screening of therapeutic agents. At least four of the agents in preclinical or early clinical development leading toward clinical trials for cancer or AIDS originally came from Japan. One of these, a benzoylphenylurea from Ishihara Sangyo, involved very active joint research in which the company provided a number of prodrugs. For many years, there also has been formal collaboration in drug development with CRC (United Kingdom) and EORTC. DTP carried out the formulation, development, and production of clomesone, bryostatin, and rhizoxin, which had their initial clinical study in Europe. These studies are aimed at determining the suitability of the compounds for testing in phase I clinical trials. DTP works with investigators in Europe and Japan who have expertise in the selection of candidate agents for screening. Project areas include cyclin-dependent kinase inhibitors (France and Germany); antiangiogenesis compounds (Italy); benzothiazoles (CRC, United Kingdom); and polymer-delivered therapeutic agents (United Kingdom).

Biological Testing Branch

The DTP Biological Testing Branch has actively worked with a number of foreign investigators in several areas. Structures of a novel class of compounds have been developed and provided to DTP for evaluation, and techniques have been created for comparative evaluation of selected compounds in vivo and in tumor systems characterized for specific molecular targets. Furthermore, collaborations with CRC and EORTC are enhanced by yearly meetings of the Screening and Pharmacology Group, EORTC, where open discussion of compounds under evaluation can take place. This cooperation has resulted in several significant joint research activities leading to identification, further development, or both, for specific compounds and for classes of compounds.

Natural Products Branch

The DTP Natural Products Branch has a program of plant collections in Africa and Southeast Asia. The work is coordinated through contracts with the Missouri Botanical Garden, St. Louis (Africa), and the University of Illinois, Chicago (Southeast Asia). In Central and South America, there are direct collaborative activities with organizations in Brazil, Costa Rica, Mexico, and Panama. Joint efforts also have been established with groups in Bangladesh, China, Iceland, Korea, Pakistan, South Africa, and Zimbabwe. Collection of marine organisms in the Indo-Pacific region is performed through contract with the Coral Reef Research Foundation. Direct cooperative studies of marine organisms have been established with groups in Australia, New Zealand, and South Africa.

License agreements have been negotiated with countries that are a source of naturally occurring biological materials found through NCI's drug-discovery program. Three compounds have demonstrated highly significant inhibitory activity in vitro against human immunodeficiency virus (HIV). Two possible anti-HIV agents, conocurvone and calanolide, were isolated from plant material obtained under the NCI Natural Products Program, from Western Australia and Malaysia, respectively. In addition, NCI provides screening results to the countries where the material was collected, as well as invitations to scientists from the source countries to join NCI-supported U.S. scientists in the study of plants and marine organisms with potential for therapeutic activity that were collected within their borders. All expenses are paid by NCI. Agreements have been reached with organizations in Bangladesh, Cambodia, Ecuador, Fiji, Gabon, Ghana, Laos, Madagascar, Malaysia, Palau, the Philippines, Tanzania, Vietnam, and Zimbabwe. Additional joint agreements are in place with the South American Office for Anticancer Drug Development, Fundaçao Oswaldo Cruz, and University Paulista, Brazil; Kunming Institute of Botany and the Hong Kong University of Science and Technology, China; Instituto Nacional de Biodiversidad, Costa Rica; the

TABLE VIII-3.

NCI Foreign Grants and Contracts, Fiscal Year 2000

Country or Area	Grants	Contracts
Australia	10	
Belgium	1	
Canada	21	
China		1
Costa Rica		1
Denmark	1	1
France	4	
Germany	1	
India	1	
Israel	4	
Italy	1	
Jamaica		1
Japan		1
Mexico	1	
The Netherlands	2	
New Zealand		1
Poland		1
South Africa	1	
Spain	1	
Sweden	2	1
Switzerland	1	
Trinidad and Tobago		1
United Kingdom	6	
Total	**58**	**9**

University of Iceland; the Korean Institute of Science and Technology; Instituto de Quimica, Mexico; H. E. J. Research Institute of Chemistry, Pakistan; Universidad de Panama; and the South African Council of Scientific and Industrial Research.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

Substantial progress has been made in many areas of basic cancer research. For example, a number of genes involved in specific cancers have been identified, and each new genetic discovery guides the development of specific diagnostic approaches, interventions, and treatments. The improving ability to detect very small tumors and to identify rapidly growing tumors is increasing the potential to treat cancer more effectively and to reduce cancer mortality.

Cancer prevention plays a growing role. There is convincing evidence that about one-third of the cases of cancer in the United States are related to the use of tobacco products and that another one-third may be related to dietary factors. One of the most dramatic advances has been the identification of specific cancer susceptibility genes that can be used to identify individuals at high risk of developing cancer. The discovery of the BRCA1 gene, which is present in patients who have an inherited form of breast cancer, is an example.

During FY 00, NCI supported 58 foreign research grants and nine foreign research contracts (Table VIII-3). Also, 126 research grants and six research contracts awarded to U.S. institutions during FY 00 had a foreign component. In addition to awards to extramural institutions, scientists in the NCI intramural laboratories are involved in many joint research projects with foreign investigators, institutions, or both. International cooperation in cancer research has played a key role in virtually all areas of progress in the fight against this disease. The projects cited in subsequent sections of this chapter are examples, not an exhaustive list, of NCI international activities.

Breast Cancer

At the University of Melbourne, Australia, NCI is supporting the establishment of a large registry of Australian multigenerational pedigrees, by collection and storage of epidemiologic information on the major recognized and putative risk factors for breast cancer and by performance of follow-up studies. This resource will be made available worldwide for research into the genetic epidemiology, biology, causes, prevention, and treatment of breast cancer. Australia is an excellent country in which to establish a Breast Cancer Family Registry. The size of the population is manageable yet sufficient for a study. Other advantages include ethnic diversity and a highly localized, relatively stable population in which families are usually intact and family members are in contact with one another.

The Study of Tamoxifen and Raloxifene, one of the largest breast cancer prevention studies ever performed, is recruiting volunteers at more than 400 centers across Canada and the United States, including Puerto Rico. The trial includes 22,000 postmenopausal women at increased risk of breast cancer. The purpose of the trial is to determine whether the drug raloxifene, for prevention of osteoporosis, is as effective in reducing the chance of developing breast cancer as tamoxifen has proven to be. Tamoxifen was shown to reduce the chance of developing breast cancer by about one-half in the Breast Cancer Prevention Trial, a study of more than 13,000 premenopausal and postmenopausal women at high risk of breast cancer.

Approximately 12% of Ashkenazi Jewish women with breast cancer are carriers of mutations in one of two cancer susceptibility genes, BRCA1 and BRCA2, both of which are associated with a very high lifetime risk of breast cancer, estimated at 57%–90%. NCI supports work by investigators at the University of Toronto, Ontario, on possible differences in the natural histories of hereditary and nonhereditary breast cancers. The investigators are identifying and evaluating 2,818 cases of breast cancer diagnosed in Israel in 1987 and 1988. Approximately 1,900 of these cases occurred in Ashkenazi Jewish women. The purpose of this study is to estimate the 10-year survival for breast cancer patients with BRCA1 and BRCA2 mutations and to compare this estimate with that for women without these mutations. DNA samples extracted from the tumor specimens will be typed for three mutations in BRCA1 and BRCA2 in Jewish persons, and investigators will obtain information about tumor size and nodal status at diagnosis, as well as demographic data about the year and place of birth, religion, and ethnic group.

Cervical Cancer

Worldwide, cervical cancer is the second or third most common cancer among women, after breast cancer. In some developing countries, cervical cancer is the most common cancer. About 400,000 new cases are diagnosed each year, predominantly among the economically disadvantaged, in both developing and industrial nations. Cervical cancer is very treatable, but only if diagnosed in its early stages. Thus, determination of risk factors and development of new detection methods are important. The primary risk factor for cervical cancer is infection with certain types of the human papillomavirus (HPV). Large studies have found HPV in more than 93% of cases of cervical cancer. Because most women infected with HPV do not develop cancer, however, researchers are looking at cofactors that may work with HPV to promote carcinogenesis.

Immunologic and other cofactors are the focus of a large NCI study in Guanacaste Province, Costa Rica, a region with high incidence of cervical cancer. Since the early

1990s, investigators have screened about 10,000 women, to obtain data on the incidence and prevalence of HPV infection and on cofactors that increase the risk of cervical cancer. Selected subcohorts numbering about 6,000 are still having follow-up. A primary aim is to understand the origins of high-grade squamous intraepithelial lesions, the direct precursors to invasive cervical cancer, and to characterize the natural history of HPV infection in this population. This work is leading to a planned phase III trial of an HPV vaccine that is under development at NCI.

Prostate Cancer

Prostate cancer is the most common cancer in U.S. men, and African-American men have the highest prostate cancer rate in the world. NCI-supported studies in several countries are addressing factors that seem to influence the incidence of prostate cancer.

Studies by NCI-supported investigators at the University of Pennsylvania, Philadelphia, are exploring whether genes that regulate the disposition of testosterone contribute to development of prostate cancer and whether these genes partly explain differences in prostate cancer rates between populations of African origin (African Americans, Ghanaians, and Senegalese) and U.S. whites. Inclusion of African populations will provide information about the possible role of environmental factors. The high incidence of prostate cancer in African-American men is also evident in other populations of West African descent, a finding that suggests the importance of genetic factors. NCI-supported investigators from the University of Pittsburgh, Pennsylvania, are studying a large group of men in Trinidad and Tobago, where risk of prostate cancer is high, the population is primarily of West African descent, and there is less admixture than among African Americans.

Data from a population-based, case–control study conducted in Shanghai, China, to investigate the reasons for the extremely low, but increasing, risk of prostate cancer in this population are being analyzed. The scientists are addressing a variety of hypotheses related to hormone levels, dietary intake, anthropometry, and medical practice, using both interviews and biological information. In addition, they are exploring whether genetic factors are related to the very low risk of prostate cancer in China.

Renal Carcinoma

Until recently, relatively little attention was paid to the genetics and histology of renal carcinomas. Improved understanding of the genetic basis of human renal carcinoma has come from studies of families with an inherited predisposition to develop this disease. Researchers in NCI's Laboratory of Immunobiology, Division of Basic Sciences, are studying the genetic basis of three of its inherited forms: von Hippel-Lindau disease, hereditary papillary renal carcinoma, and renal carcinoma associated with the chromosome 3;8 translocation. They have identified families in which multiple members have renal oncocytoma. These families have provided a foundation for studies aimed at defining genes involved in the pathogenesis of renal oncocytoma. There has been international collaboration to include clinical populations from Canada, Hungary, and Italy.

Dietary Factors

NCI scientists have been conducting a number of research projects on esophageal cancer in China, where the incidence of this malignant disease is the highest in the world. Two nutritional intervention trials, in collaboration with the Chinese Academy of Medical Sciences, were conducted in Linxian, where study findings suggest that the population's chronic deficiencies of multiple nutrients may contribute to the high incidence of esophageal cancer. Daily vitamin and mineral supplements were shown to lower cancer rates both for patients with esophageal dysplasia and for the general population. A 5-year, postintervention follow-up of these cohorts has been completed, and investigators are preparing the data for analyses of whether these early effects of micronutrient supplementation persist. Serum collected in 1985 is being used to investigate the association of micronutrient levels and some infectious agents, found by serology, with subsequent esophageal cancer, gastric cancer, and stroke in these cohorts.

Early Detection

NCI supports the work of investigators at Tata Memorial Hospital, Bombay, India, in a community-based, randomized-control evaluation of low-cost methods for early detection of common cancers in women. Breast cancer and cervical cancer account for about 50% of cancer deaths in women in India. Among the diagnostic methods being evaluated are clinical breast examination without mammography, self-examination, and visual inspection of the cervix by trained female health workers. The goal is to reduce mortality by detection and diagnosis of breast cancer and cervical cancer at an early stage. This trial is one of the first of its kind to be conducted in a developing country, and findings may be relevant to other countries and populations with limited resources (e.g., underserved populations in developed countries).

The International Prostate Screening Trial Evaluation Group is a collaboration between the researchers in Europe and North America who are conducting randomized trials of screening for prostate cancer. Countries included in the study are Belgium, Finland, Italy, the Netherlands, Portugal, Spain, Sweden, Switzerland, and the United States. The purpose of this joint research is to develop and implement an evaluation plan for the joint analysis of data from the randomized trial of prostate cancer screening, by using the blood test for prostate-specific antigen. A combined analysis offers increased statistical power and a larger, more informative database, which are advantages over an individual study. The total sample is anticipated to be in excess of 300,000 men, with a follow-up of at least 10 years.

International Consortia

In 1996, the Ministers of Health of Cyprus, Egypt, Israel, Jordan, and the Palestinian Authority formed a historic partnership, with the official signing of the Middle East Cancer Consortium (MECC) agreement. NCI played a major role in orchestrating the agreement. The aims of MECC are to increase knowledge about cancer and to decrease its burdens for the people of the Middle East. In a region where few countries maintain cancer registries, especially population-based registries, and where cancer statistics are scarce, MECC's main areas of focus include cancer surveillance, information, and education. The consortium also concentrates on training, basic research, enhancement of public health and patient

care, quality control, and international communications.

In Belfast, Northern Ireland, a Memorandum of Understanding has been signed by representatives of Northern Ireland, the Republic of Ireland, and the United States—heralding cooperation to enhance cancer research and treatment in Ireland. In Ireland, the incidence and mortality rates for cancer are among the highest in the Western world, and trinational collaboration is intended to address this problem. Initial projects are focusing on coordination of tumor registries, development of informatics to support coordinated clinical trials, and training and scholarship programs for scientists in the cancer research programs of partner institutions. The Directors of NIH and NCI, as well as leading NCI scientists in the fields of cancer surveillance and cancer treatment, participated in the All-Ireland Conference, in Belfast, in October 1999, in an exchange of information among scientists of the three countries. Multimedia medical imaging workstations have been set up to provide for the simultaneous high-resolution display of numerous modalities, using telesynergy. Specimens can be viewed remotely and concurrently from a number of sites across the Atlantic Ocean. In FY 00, NCI hosted two Cancer Epidemiology Fellows for the 1st year of a 3-year training program.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Cooperative Research Programs

Formal cooperative research programs are governed by agreements between governments or institutions. NCI participates in many of the bilateral agreements that the NIH has with some 40 nations, and NCI also has direct agreements or informal ties with institutions in many more countries.

Country-to-Country Activities and Bilateral Agreements

Australia

NCI supports studies at the Walter and Eliza Hall Institute of Medical Research, Melbourne. One project focuses on understanding the external regulation of granulocytes and macrophages at the cellular and molecular levels and on defining the molecular defects in those cells that lead to the formation of myeloid leukemia. In other NCI-supported studies at this institute, researchers are investigating (a) oncogene-induced leukemogenesis in transgenic mice and (b) molecular mechanisms by which members of the Bcl-2 oncogene family promote either cell survival or apoptosis and influence the cell cycle.

NCI also supports projects at the University of Queensland. The purpose of one study is to establish a registry of multigenerational pedigrees in Australia and New Zealand, to be used in research on the cause, pathogenesis, and prevention and treatment of colorectal cancer. Another study is focused on determining the role of the ATM (ataxia-telangiectasia mutated) protein in recognition of DNA damage. At the Peter Maccallum Cancer Institute, Melbourne, NCI is supporting studies on the role of heat shock protein 72 and related proteins in cell death.

At the TVW Telethon Institute for Child Health Research, Perth, NCI supports projects on (a) inhibiting specific oncoprotein interactions as a target for cancer therapy and (b) relating particular profiles of molecular genetic lesions to clinical outcome in pediatric acute lymphoblastic leukemia. In addition, investigators at St. Vincent's Institute of Medical Research, Victoria, are examining the process of transition from epithelial (stationary) to mesenchymal (moveable) cell classes in breast cancer metastasis.

Belgium

NCI provides partial funding to assist the EORTC Data Center, Brussels, in providing statistical assistance and expertise to the clinical cooperative groups of EORTC, which have 200 multicenter trials in progress. NCI also maintains a Liaison Office in Brussels. The International Network for Cancer Treatment Research, based in Brussels, was launched in 2000. The network, which receives partial support from NCI, has already formed a global alliance for the cure of childhood cancer and is moving ahead on other fronts.

Botswana

NCI is working with archived samples from earlier studies to examine prevalence of human herpesvirus type 8 (HHV-8) and subtypes in Bantu and among the isolated San peoples in northwestern Botswana. HHV-8 prevalence was high, and a unique subtype of HHV-8 was found in one San subject. HHV-8 is thought to be involved in development of Kaposi's sarcoma (KS).

Brazil

NCI supports an investigator from McGill University, Montreal, Quebec, who is performing an epidemiologic cohort study of the natural history of HPV infection and cervical neoplasia in a population of low-income women in São Paulo, one of the highest-risk areas worldwide for cervical cancer. Although HPV infection is known to be an important cause of cervical cancer, most of the epidemiologic data have come from retrospective studies, which do not provide information on the dynamics of cervical HPV infection in an individual. This study is testing the hypothesis that persistent infections with oncogenic HPV types are likely to be the true precursor events leading to cervical carcinogenesis. Persistence of infections is being documented by study of molecular variants of HPV, which provides a much finer level of detail than simple HPV typing. This molecular approach also may unveil other prognostic markers of progression, across the spectrum of cervical lesions. Investigators at the University of Arizona, Tucson, are using the same population for studies of nutritional status as a possible cofactor in HPV persistence and progression to cervical cancer.

NCI scientists evaluated the prevalence and distribution of HHV-8 in Brazilian Amerindians and found its prevalence to be among the highest in the world. These Amerindians are isolated from the general population, being descendants from migrations that occurred many millennia ago, and their HHV-8 is a subtype not previously described. KS has not been described in Brazilian Amerindians, but the population is small and medical care is limited.

Canada

NCI supports research projects at several Canadian universities, cancer centers, and hospitals. Efforts include studies in the following areas:

- cellular thermostability and thermotolerance;
- development of research instruments to quantify sun exposure in skin cancer research;

■ dormancy versus progression of human primary melanoma;

■ effects of exercise on quality of life in cancer patients;

■ reduction in fat intake and risk of benign breast disease;

■ molecular epidemiology of persistent HPV infection;

■ quantitation of hypoxic tumor cells;

■ development of an amorphous selenium detector for digital mammography;

■ density of tissue visualized by mammography and risk of hereditary breast cancer;

■ development of techniques for single-cell proteome analysis;

■ mechanisms of human multidrug-resistance transporter;

■ malignant stem cell in multiple myeloma;

■ studies of a new biomarker for breast cancer diagnosis; and

■ plasminogen regulation by annexin II tetramer.

At the Ontario Cancer Treatment and Research Foundation, Toronto, NCI is supporting projects on development of population-based registries of familial colon cancer and familial breast cancer. Such registries will serve as resources for future epidemiologic studies, primary prevention trials, genetic studies, and research on surveillance strategies.

NCI is collaborating with the Cancer Division of the Laboratory for Disease Control, Health and Welfare, Canada, to evaluate exposure of agricultural workers to pesticides and the impact of protective practices on these exposures. A joint project with investigators at McGill University, Montreal, is examining the association of insulin-like growth factor and the risk of prostate, colorectal, or other cancers. NCI is also working with researchers at the University of Toronto in genetic analyses of melanoma-prone families in both Italy and the United States and in functional analyses of mutations identified in these families.

NCI and the Canadian Tobacco Research Initiative jointly sponsored a workshop to identify key research questions arising from Canada's introduction of stronger warning labels on tobacco products, which will be implemented in January 2001. The introduction of the new labels presents a valuable opportunity to assess the ability of strong warning labels to change smokers' knowledge, attitudes, and behaviors regarding tobacco use.

Several Canadian institutions also participate in many of the NCI Clinical Trials Cooperative Groups and in other NCI-sponsored clinical trials.

China

NCI collaborates in many projects in China that involve research on the cause, prevention, and treatment of various types of cancer.

In Shanghai, a randomized trial of breast self-examination is under way in 435 factories of the Shanghai Textile Industry Bureau. The purpose of the study is to determine whether the regular practice of breast self-examination will reduce mortality from breast cancer. Nearly 300,000 current and retired female workers between the ages of 30 and 64 years are participating in this study. In companion studies using the same population, investigators from Fred Hutchinson Cancer Research Center, Seattle, Washington, are studying dietary factors that may influence mammary cell proliferation, mutations in BRCA1 and BRCA2 genes associated with breast cancer, and differences in cancer incidence associated with a number of occupational exposures (e.g., dyes, dusts, and fibers).

Although study findings suggest that induced abortion is associated with an increased risk of breast cancer, interpretation of results has been ambiguous, because self-reports may not accurately reflect the actual extent of abortions. For example, breast cancer patients may be more willing than others to report an abortion. Therefore, NCI-supported investigators at the Kaiser Foundation Research Institute, Oakland, California, are studying this possible relationship in Shanghai, where there is no social stigma associated with induced abortion and where family-planning records document reproductive history.

A study of biochemical and molecular early markers of lung cancer, which is the leading cause of cancer death in the United States, is being performed in a high-risk population in China. The subjects of the research are underground miners from the Yunnan Tin Corporation, who are at extraordinary risk of lung cancer from exposure to radon, arsenic, and tobacco. More than 7,000 miners receive annual screening by chest x ray and sputum cytology to identify new cases, and biological specimens, including sputum samples, are stored for evaluation of potential early markers of lung cancer. The study is being conducted jointly with scientists from the Yunnan Tin Corporation; NCI; Johns Hopkins University, Baltimore, Maryland; and the University of South Florida, Tampa.

Primary hepatocellular carcinoma (PHC) is one of the three most common causes of cancer death in the world and accounts for up to 1 million deaths per year. Little is known about the genetic epidemiology of PHC or the specific molecular mechanism responsible for the disease. The carrier rate for the hepatitis B virus (HBV), which is thought to be a causative agent of liver cancer, is very high in China (12.6%). NCI is conducting a cohort study of persons at high risk of developing hepatocellular carcinoma, in Haimen City. The study is being done in collaboration with investigators at Shanghai Medical University and Fox Chase Cancer Center, Philadelphia, Pennsylvania. The aim of the study is to identify genetic and environmental variables that place some high-risk individuals at greater risk of developing a tumor. A wide variety of genetic susceptibility loci are being examined in a nested-control design. Studies of loss of heterozygosity are being performed to determine whether genes for liver cancer exist.

In other research on PHC, a nested case–control study is being conducted in collaboration with the Qidong City Liver Cancer Prevention Program and the Zhong Shan Hospital of the 1st Shanghai Medical School. The study will correlate the genetic constitution of healthy tissue and tumor tissue in patients for whom clinical and epidemiologic information is available. The research is designed to evaluate the clinical significance of the genetic differences. Statistical methods will evaluate the role of genetics and environmental factors in PHC, and molecular studies are being conducted to determine whether genetic changes observed in tumors are consistent with a tumor-suppressor gene model of oncogenesis.

NCI is investigating the role of residential radon and other sources of indoor air pollution, such as coal combustion and wood smoke, in relation to lung cancer. The investigators are conducting a case–control study

in Gansu Province, where one-half of the population lives in underground dwellings.

In other studies, NCI is working with scientists at the Chinese Academy of Preventive Medicine to evaluate cancer risks among workers exposed to benzene. These scientists are collaborating with scientists at the Shanghai Cancer Institute and Vanderbilt University, Nashville, Tennessee, in a prospective cohort study to assess the role of occupational and environmental factors in the development of cancer in women. Case–control studies of several cancers of the digestive system are also being conducted with the Shanghai Cancer Institute.

In addition, NCI is working with researchers at the Shanghai Cancer Institute in a case–control study of the cause of cancers of the biliary tract in Shanghai, where the incidence of these cancers has been increasing. Risk factors being investigated include gallstones, bacterial infections, obesity, reproductive factors, and family history.

Several descriptive studies are planned to investigate trends in cancer rates in China and elsewhere. A joint project is planned with the Cancer Institute, Chinese Academy of Medical Sciences, Beijing, to compare mortality rates for various types of cancer in 1990–1992 with rates from an earlier exhaustive survey in 1973–1975. NCI researchers are collaborating with researchers at the Shanghai Cancer Institute to analyze cancer incidence trends in 1972–1994 in the Shanghai region and to correlate them with changes in lifestyle factors and environmental exposures.

In another NCI-supported study in Shanghai, investigators from the University of South Carolina, Columbia, are studying the interplay of hormonal, genetic, dietary, environmental, and lifestyle factors in the development of breast cancer. A related study by investigators from Louisiana State University, Shreveport, is using the same population to study the role of estrogen and insulin-like growth factors in development and progression of breast cancer. NCI-supported scientists from Rutgers University, New Brunswick, New Jersey, continue studies on accumulation of p53 protein and other early molecular events in the etiology of esophageal cancer. They are using tissue samples from patients in a high-incidence area of Henan Province.

\NCI funds the Transdisciplinary Tobacco Use Research Center at the University of Southern California, Los Angeles. The focus of this center is to prevent tobacco use among youth of diverse cultures. The investigators will conduct smoking prevention programs with middle school and high school students in California, Hawaii, and Wuhan, China, and will examine the relationship of ethnicity and acculturation to adolescent smoking.

Colombia

NCI supports scientists from Louisiana State University, New Orleans, in studies in Colombia on the role of *Helicobacter pylori* infection in development of gastric cancer. *H. pylori*–infected populations in Nariño, which are at high risk for gastric cancer, are being compared with low-risk populations in Cartagena. The scientists are looking for possible differences in characteristics of immune responses that may explain the differences in risk.

Congo

NCI is testing samples obtained in Congo (former Zaire) in 1984 from patients with KS. At that time, the etiology was unknown, but since then HHV-8 has been implicated. The focus is to examine the profile of HHV-8 antibody and viral levels. Preliminary evidence shows a high prevalence of HHV-8. Subjects who had KS were more likely to have HHV-8 detected in their blood than were persons who did not have KS but did have antibodies to HHV-8, indicating past exposure.

Costa Rica

Guanacaste Province is the site of a large NCI research project on the etiology, detection, and treatment of cervical cancer. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.") In addition, NCI is collaborating with Universidad Nacional, Heredia, to determine the relationship between exposure to pesticides and occurrence of cancer in a cohort of workers exposed to pesticides.

Czech Republic

NCI intramural scientists are collaborating with colleagues at the Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, Prague, on the following projects: (a) research on the role of methylation in downregulation of oncogene expression; (b) studies on expression of avian retroviral vectors; (c) investigation of tumor immunology and tumor rejection, particularly in relation to the antigenicity of products of the v-src oncoprotein and to the genes coding for cytokines such as interleukin 2; and (d) studies of avian leukosis virus in the duck embryo, especially the relationship of the virus to wasting disease and atrophy of the thymus gland.

Denmark

NCI supports the work of investigators at the Danish Cancer Society in research using record linkage to identify and quantify the risk of cancer associated with particular occupations and with diagnosis of selected medical conditions or treatment with certain surgical procedures. Unique opportunities to conduct cost-efficient, record-linkage studies of causes of cancer are provided by the availability of (a) population-based rosters of patients with diagnosis of various medical conditions and treatment with specific procedures and (b) cancer registry data from the same population.

A population-based, record-linkage study of cancer risk in patients with ataxia-telangiectasia and their relatives is being conducted in Denmark, Finland, Norway, and Sweden. The researchers will sequence the gene for ataxia-telangiectasia to identify and characterize mutations in patients with the condition, and they will perform screening for family-specific mutations in relatives.

NCI supports investigators at the Danish Epidemiology Science Center, Copenhagen, in studies with the long-term objective of primary prevention of non-Hodgkin's lymphoma. The scientists are conducting a nationwide, population-based, case–control study of the causal role of factors that entail modulation of the immune system. The study will be large enough to allow analyses of the influence of a variety of conditions and exposures for several distinct subgroups of lymphomas.

NCI also supports investigators from Johns Hopkins University, Baltimore, for a retrospective, population-based cohort study of risk factors for the development of "juvenile-onset recurrent respiratory papillomatosis." The investigators are using data from the Danish National Registries. This child-

hood disease, which is characterized by growth of benign papilloma in the respiratory tract, is very costly in terms of both dollars and quality of life, because repeated surgery is typical. Researchers from the University of Oklahoma, Oklahoma City, are also using data from the Danish Registries in studies of neurofibromatosis.

Egypt

Some reports have indicated a high prevalence of HHV-8 in Egypt. Using samples from subjects enrolled in studies of hepatitis C virus (HCV), NCI investigators reexamined this finding, but they found no verification that HHV-8 prevalence is high in this country.

NCI supports an investigator from the University of Texas, Houston, who is studying the influence of exposure to pesticide and other environmental factors in development of colorectal cancer in Egypt. Egypt has extensive environmental pollution and the highest incidence of colorectal cancer with early onset (younger than age 40 years) in the world. Unusual molecular characteristics of these tumors suggest a role for environmental factors.

Hepatocellular carcinoma and non-Hodgkin's lymphoma are among the long-term complications of chronic infection with HCV. NCI-supported investigators from Georgetown University, Washington, D.C., are engaged in studies of the interrelatedness among viral, genetic, and environmental risk factors for these two cancers in Egypt, where the prevalence of HCV infection is high.

Finland

Follow-up continues in the lung cancer prevention project started in Finland in 1984 as a joint effort of NCI and the National Public Health Institute of Finland. The main activity has been a study of the effects of dietary supplements of α-tocopherol and β-carotene on lung cancer incidence and mortality. Another NCI project, with the Finnish Cancer Registry, is examination of cancer risks by using data from nationwide, linked registries of disease. NCI is also collaborating with the Radiation and Nuclear Safety Authority of Finland to evaluate technology to monitor radon levels in selected homes. Using standard radon dosimetry, the scientists obtained multiple measurements of radon levels, to determine historic radon levels in these homes in Finland.

France

At IARC in Lyon, NCI provides support for the IARC Program on the Evaluation of Carcinogenic Risks to Humans. In this project, investigators use published epidemiologic and experimental data to identify chemicals or complex mixtures of chemicals that may pose a carcinogenic risk to humans. The results of data analyses are published in *IARC Monographs*. Also at IARC, NCI supports studies on (a) the role of insulin and insulin-like growth factor I in breast, endometrial, and ovarian cancer and (b) statistical methods for estimation of cancer risks associated with certain genes.

NCI is collaborating (a) with the French National Institutes of Health and Research (INSERM), Paris, France, on a study of brain cancer to evaluate risks from occupational exposures and (b) with scientists at IARC on a study of kidney cancer in several Eastern European countries. In another project, NCI is working with investigators from INSERM to develop new techniques for statistical genetic analysis. These techniques will be used to analyze data from melanoma-prone families in an NCI study and in a study by the International Melanoma Genetics Consortium. At Institut Pasteur, Paris, NCI supports studies on detection of genomic alterations by use of a "molecular combing" technique.

Germany

In Germany, NCI cooperates mainly with the German Cancer Research Center, Heidelberg, and Westdeutsches Tumorzentrum, Essen. Scientists at the research center are working with NCI-supported scientists at Georgetown University, Washington, D.C., on the development of mucosotropic vaccines against HPV and with scientists at the University of Arizona, Tucson, on the overexpression of the gene for TGF-β in cells of squamous cell carcinoma. For their work in developing and further refining the panel of in vitro human tumor cell lines that is used for screening agents for cancer treatment, the Biological Testing Branch, DTP, has received human tumor specimens from investigators at the University of Freiburg.

In collaboration with the National Institute for Occupational Safety and Health, NCI is examining the occurrence of epithelial proliferative lesions and lung cancers, by histological type, in a population of uranium miners from the Saxony region in Germany who had heavy exposure to silica, radiation, or both in the 1950s and 1960s.

With NCI support, investigators from the University of Leipzig, the University of Colorado, Denver, Stanford University, California, and Fred Hutchinson Cancer Research Center, Seattle, are participating in a novel phase II study of nonablative stem cell transplantation in patients who have hematologic malignant conditions. This "mini-transplant" procedure has been performed on more than 80 patients, by using sibling and unrelated donors. The regimen was found to be safe and minimally toxic, even in patients older than 55 years of age.

NCI supports research at the German Cancer Research Center, Heidelberg, to test a model using mice that harbor humanized mutant p53 gene sequences (p53 knock-in mice) as an experimental tool for molecular epidemiology and studies of chemoprevention and cancer therapy. This new model is designed to reflect and predict three end points more faithfully than the current mouse models: human in vivo mutagenesis, carcinogenesis, and responses to therapeutic drugs that target the p53 protein.

Greece

A recent NCI study of patients with endemic KS and control subjects in Greece showed mild immunosuppression in patients with KS compared with control subjects. The average values for both groups were within the normal range. More striking, however, were the high levels of neopterin and β_2-microglobulin, which are markers of immune activation. Thus, the major impact of immune suppression in the development of KS could be mediated through activation to produce compensatory cytokines.

India

NCI investigators work with the Indian Council on Medical Research, New Delhi, and with the following cancer centers on treatment protocols for lymphoblastic leukemia and nonlymphoblastic lymphomas: Kidway Memorial Institute of Oncology, Bangalore; Tata Memorial Center, Bombay; the Cancer Institute, Madras; and the Rotary Cancer Center, All India Institute of Medical Sciences, New Delhi. NCI also co-

operates with cancer centers in Chandigarh, Trivandrum, and Vellore.

NCI researchers are collaborating with researchers at the Trivandrum Cancer Centre on an epidemiologic study to evaluate the relationship between pesticide exposure and the risk of progression of breast cancer.

NCI provides support to investigators at the Tata Institute of Fundamental Research, Bombay, for a cohort study to assess cancer incidence by the type of tobacco product used (cigarettes, bidis, or smokeless tobacco). Use of bidis (flavored cigarettes) and smokeless tobacco is common among Indian men, and some evidence indicates that their use is also increasing in the United States. Little is known, however, about the cancer risk from these forms of tobacco.

Israel

Studies at the Weizmann Institute of Science, Rehovot, are aimed at understanding the mechanism of action of the p53 tumor-suppressor gene in its normal (wild type) and mutated forms. Inactivation of the endogenous wild-type p53 gene is associated with more than one-half of all cases of human cancer. Studies are focusing on the identification and characterization of genes involved in p53 regulation. Other NCI-supported projects at the Weizmann Institute of Science include (a) use of magnetic resonance imaging and spectroscopy as non-invasive procedures for early evaluation of breast cancer response to hormonal therapy; (b) investigation of molecular mechanisms through which the ErbB-2/HER2 oncoprotein contributes to tumorigenesis in various adenocarcinomas; and (c) magnetic resonance imaging studies of angiogenesis in ovarian cancer. An NCI-supported project at Hadassah University Hospital, Jerusalem, is exploring the possible role of the heparanase enzyme in progression of breast carcinoma.

NCI is supporting an epidemiologic study of ovarian cancer at the Chaim Sheba Medical Center, Tel Hashomer, to evaluate a broad range of potential risk factors (e.g., reproductive, hormonal, nutritional, genetic, and occupational factors).

NCI is collaborating with researchers at Bar Ilan University, Ramat Gan, and the International Fertility Institute, Ra'anana, to conduct a review of tumor pathology in men with newly diagnosed prostate cancer. The purposes of this study are to obtain better population-based estimates of the risk for prostate cancer associated with mutations of the BRCA1 and BRCA2 genes and to review the pathological characteristics of tumors containing these genes. Preliminary data suggest that the rate of BRCA founder mutations among Israeli Ashkenazi Jews with prostate cancer is approximately twice that expected in the general population.

The Jerusalem Perinatal Study established a population-based research data bank (parents and offspring) based on all births in Jerusalem, including Jews and Arab residents of West Jerusalem, in 1964–1976. Approximately two-thirds of the Jews and their offspring were refugees, from Algeria, Egypt, Iran, Iraq, Lebanon, Morocco, Syria, Tunisia, Turkey, or Yemen. The information includes demographic data on the parents, infant deaths and congenital malformations, admissions to hospitals, and obstetric complications. Data on consanguinity, antenatal health, body size, smoking, fertility, gynecologic variables, and contraceptive use were obtained by interviewing specific subsets of the mothers. This cohort may be one of the largest to include ethnic ancestry with obstetric and social data, which can link siblings and parents. With NCI support, investigators from New York University School of Medicine, New York City, are linking this database with Israel's Cancer Registry (a) for follow-up studies of malignant conditions as the parents and offspring age and (b) to prepare for the potential use of this cohort for cancer prevention trials.

NCI supports an investigator from the University of Michigan, Ann Arbor, in studies of genetic influences in the epidemiology of colorectal cancer. The investigator is studying a population from northern Israel. A novel susceptibility allele (APCI1307K) has been identified in 6% of persons of Ashkenazi Jewish descent; this allele appears to double the risk of colorectal cancer. The Israeli population is one of the few populations in which a known susceptibility allele occurs with sufficient frequency to facilitate study of how genetic risks may be modified by environmental factors.

Italy

In a joint study, scientists from NCI and the University of Milan have obtained 30 pedigrees and biological specimens on kindreds with cutaneous malignant melanoma. This material, in conjunction with a case–control study of melanoma, will provide a means to investigate a genetic component to melanoma in this Mediterranean population. Genotyping of these families is under way. The study will also investigate whether deficits in DNA repair may contribute to development of melanoma. In addition, NCI and the University of Cagliari, Sardinia, are engaged in research to evaluate cancer risks among workers who applied pesticide in a campaign to eradicate malaria. NCI also collaborates with the University of Cagliari on an ecological study of the relationship between the incidence of non-Hodgkin's lymphoma and nitrate levels in public water supplies in Sardinia.

At the European Institute of Oncology, Milan, NCI is supporting a study to examine interactions between low-dose tamoxifen and fenretinide and a set of biological markers (biomarkers) in premenopausal women with minimally invasive (in situ) breast cancer.

NCI is working with investigators at the University of Milan, the Centers for Disease Control and Prevention, and the National Institute of Environmental Health Sciences, NIH, in a study of the effects of dioxin on subjects from Seveso who were exposed to this environmental toxin after an industrial accident in 1976. A population-based study of healthy subjects from the town indicates that blood levels of dioxin remain elevated 20 years after exposure. The investigators plan to conduct a case–control study of persons with cancers that have been linked to exposure to dioxin (i.e., non-Hodgkin's lymphoma and soft tissue sarcoma). Also in Milan, a new NCI study is evaluating gene–environment interactions in the development of lung cancer and smoking addiction.

The Division of Cancer Control and Population Sciences collaborates with Istituto Nazionale Tumori, Milan, and Istituto Superiore di Sanità, Rome, to accomplish three purposes: (1) to apply demographic, back-calculation models developed by these groups to estimate U.S. cancer incidence and prevalence from mortality and survival data; (2) to reach European-U.S. consensus on methods to estimate cancer prevalence on the basis of tumor registry data; and (3) to use models developed by these groups to es-

timate complete prevalence for years before establishment of a given cancer registry.

NCI-supported investigators are using data and blood samples from a study by the Italian National Cancer Institute, Milan, in studies of dietary influences on risk of breast cancer.

In a major new initiative, NCI investigators are collaborating with Italian colleagues to learn the distribution of HHV-8 in areas with high incidence of KS and to determine the relationship between HHV-8 infection and immunity to or development of KS. A large case–control study of classic KS is being conducted in Naples, Rome, and Sicily, where the HHV-8 prevalence is high. The objective is to determine risk factors for developing KS only among subjects who are currently HHV-8 positive, thus excluding the complicating influence of factors associated with previous HHV-8 infection.

Jamaica

A joint research project of NCI and the University of the West Indies, Mona, involves a series of epidemiologic, clinical, and experimental studies to define the distribution and determinants of infection with human T-cell leukemia/lymphoma virus (HTLV) and the possible role of HTLV as a cause of cancer. An important future direction is to perform follow-up studies on infection in patients with HTLV and HIV and to use the findings in these high-risk populations to define the natural history and pathogenesis of these viruses in terms of disease outcome.

Since the early 1980s, NCI has been involved in studies of the natural history of infection with human T-cell leukemia/lymphoma virus type I (HTLV-I) and its relationship to adult T-cell leukemia/lymphoma. NCI investigators have established several prospective cohorts, particularly in Jamaica. These cohorts have matured and currently serve as a source of biological specimens for exploration of important questions in disease pathogenesis. The major emphasis is on studies to evaluate familial and genetic aspects of HTLV-I infection and associated diseases. The families in the cohort are a high-risk population suitable for continued follow-up to evaluate both environmental and genetic aspects of disease pathogenesis. NCI investigators plan to extend the family studies by developing a population-based cohort of 500 HTLV-positive and 1,000 HTLV-negative participants for comparative analyses to evaluate genetic and environmental risk factors identified in the family studies.

In a study of nearly 2,000 Jamaican women, NCI is examining potential risk factors for progression of low-grade cervical lesions that are a precursor to cervical cancer. Jamaica was chosen for this investigation because of the high incidence of cervical cancer and the high prevalence of sexually transmitted infections, particularly HTLV-I, in the general population. An earlier study in Jamaica showed that HTLV-I infection was strongly associated with development of more severe cervical neoplasia. Findings show that HTLV-I proviral DNA is detectable in cervical specimens from more than one-half of infected women. This observation suggests that direct interaction between HTLV-I and HPV, the principal cause of cervical neoplasia, could contribute to cervical tumorigenesis in women infected with both viruses. To further examine this possibility, researchers are using in situ hybridization and immunohistochemistry to evaluate tissue samples from women who have both viruses. Because infectious agents other than HTLV-I may also play a role in the development of cervical cancer, cervical epithelial specimens from the Jamaica study are also being examined for herpesviruses, chlamydia, and adeno-associated viruses.

Japan

There is extensive collaboration between the United States and Japan in therapy using boron neutron capture, particularly in treatment of malignant brain tumors and melanomas. Another area of joint research is the study of modulation of neoplasia associated with liver fluke parasites, in Nagoya.

HCV has a high prevalence in Japan, which provides a situation conducive to its study. In a cohort study, NCI-supported scientists are examining the interactions of HCV and HTLV-I in an area of Japan where both viruses are endemic. The plan is to extend and expand the preliminary studies on the natural history of HCV, to consolidate the work on the natural history of HTLV-I, and to evaluate the effect of co-infection of these two viruses.

In collaboration with the Radiation Effects Research Foundation, Hiroshima and Nagasaki, NCI is conducting epidemiologic and multidisciplinary studies of cancer risk in relation to radiation dose, among a cohort of atomic bomb survivors. Studies under way include site-specific surveys for incidence of (a) benign and malignant tumors of the thyroid gland, central nervous system, and ovary and (b) cancers of the breast, liver, colon and rectum, lung, and lymphoid tissue. In addition, the researchers are conducting case–control interview studies of patients with thyroid or colon cancer. NCI investigators are also collaborating with the National Cancer Research Center, Tokyo, to identify mutagens and carcinogens in cooked meats. In another study, NCI is working with Japanese scientists who have studied families with Werner's syndrome, to evaluate the unusual melanomas that occur in excess in persons with this condition.

Malawi

NCI supports research in Malawi by investigators at the University of North Carolina, Chapel Hill, who are studying HHV-8 associated with AIDS-related KS. HHV-8 has now been identified in all forms of KS. The mode of transmission of HHV-8 infection in Africa, where HIV is transmitted heterosexually and KS is endemic, is unknown. Molecular studies are being performed to determine the likely mode of transmission of HHV-8 in this population. A sexual route of HHV-8 transmission has been suggested by several studies in the United States, where homosexual and perinatal exposure are the predominant routes of HIV transmission.

In 1994, NCI established a large clinical trial in Malawi, which showed that vaginal cleaning with an antiseptic had no effect on the risk of HIV transmission but did lower the risk of infections and early neonatal deaths. This study enrolled a cohort of more than 2,000 HIV-infected women who delivered infants, to determine how frequently breast-feeding transmits HIV in this setting. The infants who were not HIV positive at birth and were breast-fed by HIV-positive mothers were shown to have about 1% risk of infection per month of breast-feeding after the 1st month of life. These results are being used to help the World Health Organization (WHO) to formulate policy recommendations on the advisability of breast-feeding in Africa. The same samples are being used to study viral changes in infants

infected with HIV, to better understand the opportunities for early therapy.

Studies are also under way to examine HIV infection in twins born to infected mothers in Malawi. More than 600 twin pairs have been enrolled; about 30% were born to HIV-positive mothers. These infants will have follow-up for 1 year, to determine the risk of infection in first- and second-born twins and to determine whether genetic factors influence the response to infection.

Mexico

NCI is collaborating with the National Institute of Public Health in Mexico on studies of breast cancer and stomach cancer. The breast cancer project is evaluating the relationship between cancer risk and serum levels of organochlorine chemicals, such as dichlorodiphenyltrichloroethane (DDT) and polychlorinated biphenyls (PCBs). The stomach cancer study focuses on dietary factors. At the National Autonomous University of Mexico, Mexico City, NCI supports research on use of phage-display techniques to identify novel immunoreagents for detection of HPV infection.

Because *H. pylori* infection has been identified as a risk factor for adenocarcinoma of the stomach, NCI-supported scientists at Stanford University, California, are conducting a randomized, double-blind, placebo-controlled trial to explore the effect of eradicating *H. pylori* on gastric preneoplastic lesions. This study is being conducted in Chiapas, Mexico, a region with high rates of gastric cancer and preneoplasia.

The Netherlands

The Division of Cancer Prevention is working with the Department of Public Health, Erasmus University, Rotterdam, to develop a microstimulation model designed to analyze the cost and effectiveness of various screening strategies and methods for the early detection of colorectal cancer.

Cancer risk associated with nasopharyngeal implantation of radium (Crowe method) for treatment of eustachian tube dysfunction is being evaluated retrospectively in a cohort of patients treated at a number of clinics in the Netherlands during the 1940s and 1950s.

NCI supports studies at the Netherlands Cancer Institute, Amsterdam, on the untoward influence of hypoxia in human tumors on the success of treatment via radiotherapy, chemotherapy, or surgery.

Increased attention is being given to the hypothesis that nutritional habits in childhood or adolescence, particularly energy or fat intake or both, may be associated with increased risk for prostate cancer, possibly mediated through body size, weight gain, or both during particular periods of life. An NCI-supported study by investigators at Columbia University, New York City, New York, is examining this hypothesis in a population in the Netherlands, where prostate cancer is common. Nearly 60,000 men aged 55–69 years have been recruited for this prospective cohort study of nutrition and cancer risk. A substantial portion of the Dutch population was exposed to a severe famine toward the end of World War II (1944–1945). In addition, nutrition was compromised during the economic crisis of the 1930s and in the early years of the wartime occupation, which started in 1940. A substantial number of the men in this study experienced the economic depression and the wartime events in childhood. The impact of these exposures on body size and incidence of prostate cancer will be studied, as will the association between childhood nutrition and the stage of prostate cancer at diagnosis.

Norway

NCI and the Centers for Disease Control and Prevention are collaborating with the Cancer Registry of Norway to investigate the risks of several cancers associated with serum levels of persistent organohalide chemicals, including DDT and PCBs.

NCI supports a study by scientists at Vanderbilt University, Nashville, Tennessee, on a possible role of sexually transmitted viruses as a cause of testicular cancer. This case–control study is nested in a well-defined cohort of men who donated blood samples as part of the JANUS project in Norway. The JANUS project, which was sponsored by the Norwegian Cancer Society, was established in 1973 for the purpose of prospectively collecting serum to be used in epidemiologic studies of cancer development and cardiovascular disease. All blood donors to the JANUS serum bank are annually linked, through a unique, individual identification number, with the Cancer Registry of Norway.

NCI also supports a U.S. investigator for studies in Norway on the role of perinatal and intrauterine factors that may influence future risk of breast cancer in the fetus.

Panama

Serological studies have found the human T-cell leukemia/lymphoma virus type II (HTLV-II) to be endemic in some isolated Indian tribes of the Amazon and other regions in the Americas. This finding suggests that HTLV-II is an ancient virus that entered the Western Hemisphere with human migration. NCI is conducting studies on the transmission of HTLV-II and its effects on health among the Guaymi Indians residing in Changuinola, the capital of the Bocas del Toro province in Western Panama.

Peru

NCI researchers are working with Universidad Peruana Cayetano Heredia, Lima, on a descriptive study of recent changes in the incidence and pathology of esophageal cancer and stomach cancer in Peru.

Poland

NCI is collaborating with investigators at the Institute of Oncology, Warsaw, to explore the role of diet as a cause of gastric cancer, which occurs at unusually high rates in Poland. Another study is examining smoking and infection with HPV as cofactors associated with the risk of cervical cancer.

NCI researchers are working with researchers at Marie Curie-Sklodowska University, Lublin, in a population-based study to assess both environmental and genetic risk factors for breast cancer among women living in two major cities in Poland: Lodz and Warsaw. Primary areas of interest will be the relationship of risk to physical activity, alcohol consumption, active and passive smoking, occupational exposures, and dietary patterns, as well as the influence of genetic factors on these relationships. The study will also evaluate the influence of genetic susceptibility on the effects of more established risk factors for breast cancer, such as reproductive and hormone-related factors. In addition, NCI is conducting a joint study to identify causative factors associated with the high prevalence of

stomach cancer in Poland. Other cooperative efforts include molecular studies of lung and laryngeal cancer in regions of Poland with severe industrial pollution.

Although Polish women have a relatively low incidence of breast cancer, studies of Polish immigrants show that there is a rapid transition to rates seen in the host country. This finding suggests that modifiable environmental factors may help to determine risk of breast cancer. Consequently, NCI-supported investigators at Michigan State University, East Lansing, are comparing several dietary factors in Polish natives of Warsaw and in Polish immigrants to the United States.

Russia and Other Countries of the Former Soviet Union

NCI researchers and colleagues from the Jonsson Cancer Center, Los Angeles, California; Dana Farber Cancer Center, Boston, Massachusetts; and Roswell Park Cancer Center, Buffalo, New York, are participating in clinical trials based in Moscow, Russia. Two of the trials use 5-fluorouracil plus leucovorin in the treatment of colorectal carcinoma, and a third uses granulocyte colony-stimulating factor in adjuvant therapy for breast cancer.

NCI investigators are evaluating the relationship between thyroid disease, especially thyroid cancer, and doses of radiation to the thyroid from exposure to radioactive iodine and other radionuclides that were released in the 1986 nuclear power plant accident at Chernobyl, Ukraine. Leukemia risk is being studied among cleanup workers in Ukraine, and cancer incidence is being evaluated among former Chernobyl cleanup workers in Estonia, Latvia, and Lithuania. Also, NCI is cooperating with WHO, the European Commission, and the Sasakawa Memorial Health Foundation of Japan to jointly support repositories of thyroid tissue in Belarus, Russia, and Ukraine—unique resources that are maintained for the world scientific community.

NCI is working with Japanese and Russian scientists in epidemiologic studies of cancer risk among plutonium workers at the Mayak weapons fabrication plant near Chelyabinsk, Russia, and among residents of the Techa River area, in relation to exposure to radionuclides that entered the river from the plant. In addition, NCI is performing a joint study with the St. Petersburg Medical Academy for Postgraduate Training, to evaluate occupational factors as a cause of lung cancer and their interaction with genetic susceptibility markers. In a related study, the prevalence of thyroid nodules and cancer in relation to radiation dose is being studied in a cohort of 2,500 residents of Semipalatinsk, Kazakhstan, who were present as children during a period of substantial radioactive fallout from atomic bomb tests in 1949–1956.

Senegal

NCI supports research by an investigator from the University of Washington, Seattle, on cervical neoplasia and HIV infection in Senegal. This research focuses on the roles of human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) as risk factors for cervical cancer and its precursor lesions, in this region of the world where people are at very high risk of contracting HIV. Related studies are concerned with the contribution of HPV to the development of cervical cancer. Cross-sectional studies have shown HIV infection to be associated with an increased risk of HPV-related lesions.

An NCI-supported study in Senegal, where the incidence of PHC is high, is using molecular and biochemical methods to identify viral, genetic, and environmental factors associated with increased risk of developing PHC. This research is being conducted by investigators from Fox Chase Cancer Center, Philadelphia, Pennsylvania. Even though chronic HBV infection is associated with 80% of the cases of PHC in the world, 75% of chronic carriers of HBV do not develop PHC and at least one-half do not develop liver disease. Little is known about the specific environmental, viral, or genetic factors that affect risk of these diseases and how these factors interact.

Singapore

NCI supports an investigator from the University of Southern California, Los Angeles, who is conducting a cohort study of 60,000 Chinese residents of Singapore, aged 45–74 years. The primary aim of the study is to definitively establish the causal relationship between ingestion of Chinese salted fish and similar foods and development of nasopharyngeal carcinoma, as suggested by previous case–control studies. A broader aim is to establish a stable cohort for the long-term study of the relationship of dietary and other environmental determinants to cancer and other chronic diseases.

Prostate cancer is unusual in that clinically latent lesions that do not pose a health threat can be histologically indistinguishable from clinically important lesions. Identification of risk factors that predict advanced disease is thus very important. One possible indicator may be a particular polymorphism in the androgen receptor gene, which may be associated with advanced prostate cancer risk in U.S. whites. Another NCI-supported investigator at the University of Southern California is studying this possible relationship in a genetically homogeneous Chinese population in Singapore.

Slovenia

Considerable controversy surrounds the question of whether the two types of asbestos (amphilboles and chrysotile) have different carcinogenic potencies. This issue has been difficult to address because of a lack of quantitative data to estimate separate dose–response curves for the two fiber types. An NCI-supported study by an investigator from the University of Massachusetts, Lowell, is examining risk for lung cancer and for mesothelioma in former employees of a Slovenian asbestos plant. In this study, excellent data on historical exposure to each of the two broad classes of asbestos fibers are available.

South Africa

NCI is sponsoring research by an investigator from Boston University, Massachusetts, who is studying the relationship between use of hormonal contraceptives and development of invasive cervical cancer. Carcinoma of the cervix is causally linked to infection with specific oncogenic types of HPV, but not all infected women develop cancer. Previous research suggests that injectable progestogen-only contraceptives (IPCs), combined estrogen–progestogen oral contraceptives (COCs), or both may act as cofactors with HPV as a cause of cervical cancer. Evidence also suggests that IPCs may reduce the risk of cervical cancer. A 4-year, case–control study is being conducted in Cape Town, where 500 patients with invasive cervical cancer and 1,500 control subjects admitted to the two main tertiary care

hospitals are being studied. South Africa is an ideal country for testing these hypotheses, because exposure to IPCs and COCs is common, as is invasive cervical cancer.

NCI and the National Institute of Occupational Safety and Health are conducting a pilot study with the National Center for Occupational Health, Johannesburg, to identify biomarkers and susceptibility factors in the development of lung cancer among miners.

The University of Pretoria is one of the institutions participating in NCI clinical trials as part of the Eastern Cooperative Oncology Group.

Spain

Informal cooperation between NCI and scientists in Spain focuses on (a) signal transduction pathways activated by growth factors and their modification in human cancer; (b) evaluation of high-dose chemotherapy regimens followed by autologous bone marrow transplantation as therapy for patients with acute lymphoblastic leukemia or malignant lymphomas; and (c) elucidation of the cell biology of Ewing's sarcoma and related primary tumors.

NCI and Institut Municipal d'Investigacio Medica, Barcelona, are jointly evaluating the role of occupational exposures and gene–environment interactions in the development of bladder cancer.

NCI supports research of an investigator at the University of Salamanca on the role of Vav family oncoproteins in cell signaling and cancer. Several lines of evidence demonstrate that the function of Vav proteins is crucial for mounting effective developmental and mitogenic responses. Among other roles, recent results have implicated the Vav pathway in the pathogenic cycle of human lymphotropic viruses such as HIV and HTLV.

Sweden

Although activity of sex hormones undoubtedly plays a role in breast and endometrial cancers, only one-half of all breast cancers are explained by hormone-related factors, such as nulliparity, late age at first birth, early menarche, late menopause, long-term use of oral contraceptives or hormone replacement therapy, or first-degree family history of breast cancer. NCI-supported investigators at Karolinska Institute, Stockholm, are therefore examining the role of genetic factors—specifically, how variants of genes for enzymes involved in estrogen metabolism affect the risk for these two important hormone-related cancers in women. The research holds promise for better definition of individual susceptibility to these cancers and, thereby, for the possibility of selective advice to improve cancer prevention.

NCI investigators are collaborating with colleagues from Karolinska Institute in studies to explore the risk of prostate cancer after benign prostatic hyperplasia and to examine the reasons for apparent low rates of breast cancer after breast-reduction surgery.

Data from two Swedish censuses (1960 and 1970) have been linked together and to the nationwide cancer and population registries, for study of occupational risk factors for specific cancers. In addition to analysis of risk from specific occupations and industries, matrices of job exposure have been developed to analyze risk from lack of physical activity and from exposure to pesticides, solvents, sunlight, and electromagnetic fields. Data from a case–control study of rare childhood cancers are also being analyzed. The medical data come from linkage of records in the Swedish birth registry, cancer registry, and hospital registry to data on all case patients, matched control subjects, and the mothers and siblings of all case patients and control subjects. A familial aggregation study is now being planned that will similarly link data on case patients and control subjects and all family members to data from the Swedish cancer and hospital registries, for study of the possible connection between malignant lymphoproliferative diseases and autoimmune diseases in family members.

Trinidad and Tobago

NCI investigators working with the Caribbean Epidemiology Center, Trinidad and Tobago, are continuing studies on the prevalence of HTLV-I and HIV infection in the healthy population in Trinidad and Tobago. The purposes of the research are (a) to systematically obtain samples and data on lymphoreticular malignant disease, (b) to develop and follow cohorts at high risk for HIV (e.g., homosexual men and male and female prostitutes), and (c) to evaluate risk factors related to viral infection and disease outcome, with particular emphasis on interaction of HTLV-I and HIV.

The high incidence of prostate cancer in African-American men is also evident in other populations of West African descent. This finding suggests the importance of genetic factors. NCI-supported investigators from the University of Pittsburgh, Pennsylvania, are studying a large group of men in Trinidad and Tobago, where risk of prostate cancer is high, the population is primarily of West African descent, and there is less admixture than among African Americans.

Turkey

A hospital-based, case–control study of several cancers is being conducted in collaboration with the Social Security Agency Hospital, Istanbul, to identify occupational causes of cancer in Turkey.

United Kingdom

Cooperation continues between NCI and British scientists, particularly in the field of radiotherapy. Clinical trials of fast-neutron therapy have long been supported at Clatterbridge Hospital, Merseyside, England; the University of California, Los Angeles; M. D. Anderson Cancer Center, Houston, Texas; and the University of Washington, Seattle. These NCI-supported trials are the only ongoing phase III studies in the world that are designed to evaluate the use of neutrons in the treatment of cancers of the prostate, lung, and head and neck.

At the University of London, England, NCI supports studies on (a) prediction of human tumor response by using magnetic resonance spectroscopy with 31P, (b) development of noninvasive measurements of thymidylate synthase inhibition, and (c) radionuclide therapy for skeletal metastases.

At the University of Glasgow, Scotland, NCI supports research on identification of modifications to specific DNA sequences that are rich in CG nucleotides and that may occur during the earliest stages of breast cancer.

NCI-supported investigators in the United States and colleagues at St. Bartholomew's Hospital, London, England, are collaborating in development of a specimen bank for identification of serological markers for ovarian cancer.

Vietnam

In the absence of direct evidence of benefit, adjuvant ovarian ablation is a controversial therapy for ovarian cancer. Since 1993, NCI

has supported investigators from the University of Wisconsin, Madison, who are conducting a randomized, controlled trial of surgical oophorectomy plus tamoxifen (to preserve bone density) versus tamoxifen alone to prevent recurrence of breast cancer. The investigators are studying premenopausal Vietnamese women with TNM stage II–IIIA carcinoma of the breast. In 1997, two centers in coastal China joined the trial. Adjuvant therapies of any kind have not been widely available to these populations.

Zambia

Studies have identified HHV-8 in almost all KS tissues and in lymphomas in the body cavity. This virus may play an important role in the transformation and development of KS. One of the many pertinent questions about this virus is its route of transmission. NCI supports research by investigators at the University of Nebraska, Lincoln, in collaboration with the University of Zambia Medical School, Lusaka, to study the causes of KS. Zambia has a very high incidence of HIV infection in women and children; moreover, KS constitutes about 20%–25% of the malignant conditions seen in Zambian infants and children. These rates provide a unique opportunity to explore the possible vertical transmission route of HHV-8 and whether HHV-8 infection leads to development of KS in children. The researchers have already found that Zambian infants and children with KS carry HHV-8 DNA sequences and that many pregnant Zambian women who are healthy or who are infected with HIV-1 are also infected with HHV-8.

Taiwan

Information exchange continues between scientists in the United States and Taiwan on diseases endemic to that part of the world: hepatitis due to HBV, nasopharyngeal carcinoma, and T-cell leukemia.

Since 1989, NCI has collaborated with the National Taiwan University, Taipei, and the National Institute of Dental and Craniofacial Research, NIH, on studies of genetic, viral, and environmental factors as causes of nasopharyngeal carcinoma. This work includes a completed case–control study of nasopharyngeal carcinoma in Taipei and a new country-wide effort to enroll high-risk families in a study to investigate the role of inherited predisposition and genetic and environmental factors in this disease.

Multinational Studies

Second malignant neoplasms are being studied among 1-year survivors of testicular or ovarian cancer reported to population-based cancer registries in Canada, Denmark, Finland, the Netherlands, Sweden, and the United States. A cohort survey will characterize risk of a second cancer, by age and time since treatment, and a nested case–control study is expected to evaluate and quantify leukemia risk associated with specific therapies. In a separate study, population-based cancer registries in these countries are being used to study second cancers in patients with Hodgkin's disease treated by radiation or other therapeutic regimens.

Cancer risk is being evaluated in a cohort of 20,000 patients who received bone marrow transplantation for leukemia, aplastic anemia, or other diseases, in 1964–1992. Data are being obtained from the United States and from 234 transplant teams in more than 50 countries that report data to the International Bone Marrow Transplant Registry in Wisconsin. A cohort study has been conducted, and analyses are ongoing. A nested case–control study in this cohort is being performed to obtain information on treatment and cancer risk factors that is not available from the computerized files on the cohort.

Thyroid cancer data from 14 case–control studies conducted in Italy, Japan, Norway, Sweden, Switzerland, and the United States are being analyzed together, to clarify associations between hormonal, medical, and environmental risk factors and thyroid cancer.

NCI has joined the International Testicular Cancer Linkage Consortium, which is coordinated by the Institute for Cancer Research, Haddow Laboratories, Sutton, England. This consortium includes investigators from Australia, Germany, the Netherlands, Scandinavia, the United Kingdom, and the United States. Its mission is to map and clone the cancer susceptibility genes that predispose to the development of hereditary testicular cancer.

To facilitate the understanding of mammalian development, infectious disease, and neoplasia and to provide a balance to biological exceptions that may occur in rodent modeling of human genetics, scientists in the NCI Laboratory of Genomic Diversity are developing a comparative genetic map of the domestic cat, in the Feline Genome Project. The cat is an attractive candidate for laboratory genetics for several reasons, including abundant polymorphic morphological loci, heritable defects homologous to those that cause human genetic diseases, and epidemics of two viruses that cause neoplasias and immunodeficiencies—feline leukemia virus and feline immunodeficiency virus, respectively. Insights gained from these studies have helped in exploration of new mechanisms for immune and natural defenses against fatal infections and neoplastic diseases. These studies have involved collection and analysis of samples from Africa, Asia, and South America.

NCI is funding efforts to establish a multicenter clinical trials group, the Proton Radiation Oncology Group (PROG). PROG will initially include three U.S. facilities and will develop protocols to determine whether the clinical application of proton beams is superior to the best current methods of radiotherapy with photons or electrons, for patients with tumors at select anatomic sites. Foreign investigators from proton facilities in France, Japan, Russia, South Africa, Sweden, Switzerland, and the United Kingdom will be encouraged to participate in the PROG research efforts, and this collaboration will enhance the level of research on proton therapy, through improved communications and increased accrual of participants in clinical trials over shortened periods.

The NCI Applied Research Program administers the International Breast Cancer Screening Network, a voluntary consortium of 25 countries that have active programs for population-based screening by mammography, to detect breast cancer. This network is dedicated to joint research aimed at identifying and fostering efficient and effective approaches to worldwide control of breast cancer through population-based screening mammography. Detailed information on the consortium and specific activities of working groups is available at http://www-dccps.ims.nci.nih.gov/ARP/ibsn.html.

The European Commission has funded a study to explore the association of dietary patterns and the incidence of various cancers within four cohorts from Finland, Italy, the Netherlands, and Sweden. NCI and

Finnish investigators are participating in this study, with a focus on analyses related to lung cancer within an existing cohort in Finland. Research from this international collaboration is intended to develop common statistical and methodological approaches and to gain insight into the dietary patterns and risk factors that consistently influence the occurrence of various types of cancer across countries. In related efforts, NCI maintains the Dietary Assessment Calibration/Validation Register, a web-based register of studies and publications that compare estimates of dietary intake from two or more dietary assessment methods (http://www-dacv.ims.nci.nih.gov/). The register was developed as a means of keeping the international nutrition and health community aware of calibration/validation studies on dietary assessment methods being conducted worldwide.

NCI has provided partial support for the Global Youth Tobacco Survey, a school-based survey developed by WHO and the Centers for Disease Control and Prevention. The survey aims to determine the prevalence of tobacco use among students aged 13–15 years and their knowledge, attitudes, and behaviors regarding tobacco use. Participating nations will have an enhanced capacity to design, implement, and evaluate tobacco control and prevention programs. NCI funding permitted 35 additional countries to implement the survey in FY 00.

HHV-8 is thought to be more prevalent in Mediterranean areas than in northern Europe, but some recent reports suggest that there are pockets of HHV-8 in northern Europe (Faroe Islands and Iceland). NCI is therefore examining a large collection of sera from diverse Nordic countries to determine whether there are foci of HHV-8 within these populations and to investigate the reasons for such a distribution. Initial findings suggest only a low prevalence of HIV in most areas of Scandinavia.

With NCI support, investigators from Canada (7 institutions), Germany (3 institutions), and Denmark (1 institution) are collaborating with investigators from 29 institutions in the United States on a novel phase III clinical trial of therapy with MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) in organ-confined bladder cancer, as evidenced by the p53 status of the cancer. This is the only phase III trial in which patients are randomly assigned to therapy on the basis of the p53 status of the tumor.

Between 1985 and 1989, NCI conducted the Multicenter Hemophilia Cohort Study, which prospectively evaluated, on a regular basis, more than 2,000 persons with hemophilia attending comprehensive clinics in Austria, Germany, Greece, Switzerland, and the United States. In FY 00, NCI initiated the Second Multicenter Hemophilia Cohort Study. During 2001, this study will enroll and begin prospective annual evaluation of approximately 4,500 persons with hemophilia attending clinics in Austria, Brazil, Canada, France, Germany, Greece, Italy, Sweden, the United Kingdom, and the United States. The primary objective is to characterize the natural history of HCV infection, how HCV interacts with HIV, and how HCV affects risk of cancer and other diseases.

NCI is engaged in laboratory collaborations with investigators in Canada, Germany, and the Netherlands on various inherited pediatric syndromes that predispose to the development of leukemia and various solid tumors. Similar joint research projects are being developed with investigators in Canada, Germany, Israel, Italy, the Netherlands, South Africa, and the United Kingdom.

A critical goal for prevention research is the application of new technologies for the detection of biomarkers to identify human disease and, perhaps more important, to identify individuals at high risk or predisposition to develop a particular disease. NCI is funding several laboratories for development of biomarkers, as part of the Early Detection Research Network. A set of cooperative agreements have been signed to establish this Network for the development, evaluation, and validation of biomarkers for earlier cancer detection and risk assessment. Two of the developmental laboratories are in Canada—at the University of British Columbia, Vancouver, and the University of Toronto, Ontario. The third international laboratory is at Oxford Glycobiology Institute, England.

With NCI support, investigators at the John Wayne Cancer Institute, Santa Monica, California, are leading four randomized, multi-institutional, phase III clinical trials in melanoma. One phase III trial is determining whether wide excision of the primary cancer by using intraoperative lymphatic mapping, followed by selective lymphadenectomy, will prolong overall survival for a longer duration than wide excision of the primary melanoma alone. Overseas institutions assigning patients to this protocol include three Australian sites, one site in Canada, one site in Italy, and two sites in the Netherlands. The other three phase III clinical trials are testing the polyvalent allogeneic melanoma vaccine, CancerVax, in patients with stage II, III, and IV melanoma, respectively. Countries involved in these trials include Australia, Canada, France, Israel, Italy, the Netherlands, Norway, and the United Kingdom.

NCI partially supports the International Bone Marrow Transplant Registry (71,000 cases) and the Autologous Blood and Marrow Transplant Registry (62,000 cases), where transplant centers from 44 countries all over the world submit data on blood and marrow transplant cases.

Activities With International and Multinational Organizations

OIA is NCI's liaison with international agencies involved in cancer research and prevention. OIA also maintains connections with premier cancer centers worldwide and with organizations that have international components.

European Organization for Research and Treatment of Cancer

NCI's collaborative program with EORTC and with CRC in the United Kingdom remains highly successful in providing a regular flow of new compounds for NCI's automated assay for screening potential anticancer and anti-AIDS agents. The therapeutic potential of these agents is tested in a panel of in vitro human tumor cell lines. The collaborative program also provides new drugs for phase I and II clinical evaluations.

EORTC joins some 2,000 European cancer specialists in 250 institutions into a single working team. The EORTC Data Center, Brussels, provides the statistical and data-processing services required for state-of-the-art clinical trials. EORTC provides NCI with early access to results from cancer research supported by the European Community.

International Agency for Research on Cancer

IARC, an organization in Lyon, France, that is affiliated with WHO, has 18 member countries: Argentina, Australia, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Norway, Russia, Sweden, Switzerland, the United Kingdom, and the United States. Among NCI-supported projects at IARC is the publication of a monograph series evaluating the carcinogenic risks of chemicals to humans. These IARC Monographs are used as authoritative sources of information by governments and regulatory bodies worldwide. NCI represents the United States on the Governing Council of IARC. The U.S. portion of IARC's regular budget is provided by the U.S. Department of State.

International Union Against Cancer

UICC, which is based in Geneva, Switzerland, is a worldwide organization with more than 250 members in 84 countries. NCI provides partial support to the UICC Committee for International Collaborative Activities, the UICC Detection and Diagnosis Program, and the UICC Fellowship and Personnel Exchange Program, which receives funding for International Cancer Technology Transfer fellowships. More than 100 short-term fellowship awards were made during FY 99.

Organization of European Cancer Institutes

The Organization of European Cancer Institutes was founded in 1978 to foster cooperation among cancer centers of the Economic Community and the Warsaw Pact countries. With the disintegration of the Warsaw Pact, interaction among cancer centers in the United States, Central and Eastern Europe, and Western Europe has improved greatly. OIA represents NCI at the annual general assembly meetings of the Organization of European Cancer Institutes.

Pan American Health Organization

PAHO has been the recipient of an OIA contract that contributes to the support of the Latin American Cancer Research Information Project. PAHO has also been involved in translation of an oncology textbook and an elementary school health curriculum. (See also the section on "Cancer Information Dissemination.")