NATIONAL CANCER INSTITUTE
Women's Health Report, Fiscal Years 2001-2002
March 2003

EXECUTIVE SUMMARY

This report describes many of the activities and accomplishments of the National Cancer Institute's (NCI's) research programs in fiscal years 2001 and 2002, addressing cancers specific to or primarily affecting women, as well as those cancers with high incidence or mortality among women. Included are breast, cervical, ovarian, endometrial, colorectal, lung and other tobacco-related cancers, as well as AIDS (acquired immunodeficiency syndrome)-associated malignancies.

Please note: Incidence and mortality statistics reported for 2003 will be age-adjusted to the 2000 U.S. population standard. Previous statistics based on the 1970 population standard should not be compared to new data generated from 2000 age-adjusted population standard. Additionally, some of the rates, particularly for different racial/ethnic groups, will be changed as the new statistics are calculated.

Cancer continues to take a devastating toll on American women. By the end of 2003, an estimated 658,800 women will have been diagnosed with cancer, and approximately 270,600 women will have died of the disease. Despite these grim statistics, our nation is making important progress in the fight against cancer. In the 1990s, cancer incidence rates for all cancers decreased for men and remained relatively stable for women. Cancer mortality rates for both women and men declined through the 1990s. However, lung cancer mortality rates for women have been increasing. Breast cancer incidence rates showed little change in the 1990s, but death rates have declined by about 3 percent of January 1999, there were 8.9 million people, or 3 percent of the U.S. population, who were cancer survivors, and 56 percent of these survivors were women.

NCI is committed to continuing efforts to reduce the toll of cancer through scientific discovery and its application to people. In 2000, NCI formally established an Office of Women's Health. Organizationally located within the Office of Science Planning and Assessment, the Office of Women's Health is responsible for assisting in planning, evaluating, and coordinating activities related to cancers in women. Among the other programs and activities in NCI that focus on women's cancers are the Breast and Gynecologic Cancer Research Group in the Division of Cancer Prevention, and the multidisciplinary Breast Cancer and Gynecologic Malignancies Faculties of NCI intramural researchers. NCI staff participate in multiple, diverse relevant scientific partnerships and collaborative activities with other federal and non-federal scientists.

NCI supports and coordinates broad-based research programs investigating all aspects of cancer in men and women. Through its strategic planning process, NCI has identified many of the questions that need to be answered, areas of research and care that need to be further investigated, and infrastructure that needs to be strengthened to advance our knowledge in the study of cancer. By focusing research on areas with high potential, we have the opportunity to accelerate the pace of discovery and facilitate the translation of research knowledge to clinical application. The strategies are outlined in *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2004* (http://plan2004.cancer.gov/budget/2004) and include descriptions of areas that will advance discovery and its application and address areas of public health emphasis. As part of the planning process, NCI convenes Progress Review Groups (PRGs) to assist in setting priorities for organ site-specific research. Between 1998 and 2002, 10 PRG reports were completed including breast, colorectal, lung, and gynecologic cancers. Following release of the reports, NCI develops strategic plans for implementing PRG recommendations. Reports for all completed PRGs, strategic plans, and additional information are available at http://prg.nci.nih.gov.

To develop more effective approaches to cancer prevention, early detection, and treatment, we need to better understand the interactions between inherited genetic and environmental factors. Consortia and resource networks bring multidisciplinary researchers together to pool data and resources for large population studies. For example, NCI Breast and Ovarian Cancer Family Registries and the Cancer Genetics Network provide resources for characterizing predisposing genes in high-risk families. Increasing knowledge of the molecular changes that cause cancer enables us to identify potential targets for prevention and treatment drug discovery. New technologies help to define the molecular signatures of cancer cells and the microenvironment with which they interact. Recent exciting

advances in proteomics have resulted in a new procedure for recognizing patterns of protein expression in normal and cancerous blood samples. A test for early detection of ovarian cancer using proteomics is now in clinical trials.

Advances in imaging and biosensor technologies are resulting in improved cancer detection, diagnosis, and treatment through the development of novel imaging agents, improved functional imaging methods, and the development of molecular and digital imaging databases. Investigators are studying the use of digital mammography to enhance the interpretation of conventional mammography. Tools such as ultrasound, molecular resonance imaging, and positron emission tomography are being studied for their potential to improve the accuracy of screening and diagnosis of breast and other cancers.

Ongoing and planned initiatives support research to understand disease and treatment-related effects and develop effective interventions to improve quality of life and disseminate clinical guidelines to improve quality of care. Numerous initiatives focus on research on the social, cultural, environmental, biological, and behavioral determinants of cancer, and how they contribute to disparities in cancer care and prevention in population groups that are disproportionately impacted by cancer. For example, The Center to Reduce Cancer-Related Health Disparities (CRCHD) has identified as a high priority, the need to understand and reduce the high rate of cervical cancer mortality in some regions of the United States. During 2001and 2002, the CRCHD has consulted with experts from these regions and from other federal and state health agencies to develop interventions that ultimately reduce this preventable cancer.

The devastating impact of tobacco use and exposure to tobacco is being addressed by studies to better understand the genetic and environmental factors involved in tobacco addiction, screening trials in current and former smokers, clinical research to identify behavioral and pharmaceutical interventions for prevention and treatment of addiction, and better treatments for tobacco-related cancers. NCI has taken the lead in a public/private partnership effort to address the high rate of tobacco-related cancers in women and adolescent girls. Recommendations from a priority setting meeting held in early 2003 will provide the basis for the development of action plans to increase our understanding of the sex-based differences in women's smoking behaviors, susceptibility to tobacco addiction and tobacco-related cancers, and translation of current knowledge to effective prevention and treatment interventions.

NCI supports a broad program of clinical research to develop new agents and novel approaches for the prevention, early detection, and treatment of cancer. Clinical trials to evaluate improved and novel prevention, detection, and treatment strategies are carried out within a clinical trials infrastructure that includes NCI Cancer Centers, Cooperative Clinical Trials Groups, Specialized Programs of Research Excellence, and the Community Clinical Oncology Program (CCOP) and Minority-based CCOPs.

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INTRODUCTION

This report describes many of the activities and accomplishments of the National Cancer Institute's (NCI's) research programs in fiscal years 2001 and 2002, addressing cancers specific to or primarily affecting women, as well as those cancers with high incidence or mortality among women. Included are breast, cervical, ovarian, endometrial, colorectal, and lung and other tobacco-related cancers, as well as AIDS (acquired immunodeficiency syndrome)-associated malignancies.

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NCI is committed to continuing efforts to reduce the toll of cancer through scientific discovery and its application to people. In 2000, NCI formally established an Office of Women's Health. Organizationally located within the Office of Science Planning and Assessment, the Office of Women's Health is responsible for assisting in planning, evaluating, and coordinating activities related to cancers in women. Among the other programs and activities in NCI that focus on women's cancers are the Breast and Gynecologic Cancer Research Group in the Division of Cancer Prevention, the multidisciplinary Breast Cancer and Gynecologic Malignancies Faculties of NCI intramural researchers. NCI staff participate in multiple, diverse relevant scientific partnerships and collaborative activities with other federal and non-federal scientists.

NCI supports a number of broad-based research programs that apply to all types of cancer in both women and men. Through its strategic planning process, NCI has identified many of the questions that need to be answered, areas of research and care that need to be further addressed, and infrastructure that needs to be strengthened to advance our knowledge in the study of cancer. By focusing research on areas with high potential, we have the opportunity to accelerate the pace of discovery and facilitate the translation of research knowledge to clinical application. The strategies are outlined in *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2004,* http://plan2004.cancer.gov/budget/2004.htm. As part of the planning process, NCI convenes Progress Review Groups (PRGs) to assist in setting priorities for organ site-specific research. Between 1998 and 2002, 10 PRG reports were completed for cancers including breast, colorectal, lung, and gynecologic. Following release of the reports, NCI develops strategic plans for implementing PRG recommendations. Reports for all completed PRGs, strategic plans, and additional information are available at http://prg.nci.nih.gov.

CROSSCUTTING INITIATIVES

TRENDS IN CANCER

Accurate information on the incidence and impact of the disease is critical to decision making in science and public health. For this reason, NCI has established a number of programs and initiatives to provide infrastructure, track trends, and report cancer statistics. In the 1990s, NCI's surveillance efforts were expanded to cover a broader spectrum of the racial, ethnic, socioeconomic, and cultural diversity of our country. These include:

- $ The **Surveillance Research Program**, http://surveillance.cancer.gov/.
- $ **Surveillance, Epidemiology, and End Results (SEER) Program**, http://seer.cancer.gov.
- $ **Atlas of Cancer Mortality in the United States, 1950–94**, http://www3.cancer.gov/atlasplus/.
- $ **Cancer Intervention and Surveillance Modeling Network (CISNET)**, http://cisnet.cancer.gov.

CANCER BIOLOGY AND GENETICS

Basic research studies exploring the science of how cancer develops form the foundation of cancer research. Identifying, at the molecular and cellular level, the fundamental processes that underlie a cell's normal development and transformation from normal to premalignant to malignant can lead to new prevention, detection, and treatment approaches. NCI has established a number of initiatives to provide infrastructure and stimulate interdisciplinary research in order to make progress. These include:

- $ **Specialized Programs of Research Excellence (SPOREs)** (including 9 in breast cancer and 4 in ovarian cancer), http://spores.nci.nih.gov
- $ **The Cancer Genetics Network (CGN)**, http://epi.grants.cancer.gov/CGN/
- **The Cancer Family Registries** (CFRs), http://epi.grants.cancer.gov/CFR/
- $ **Cancer Genome Anatomy Project (CGAP)**, http://cgap.nci.nih.gov
- **Early Detection Research Network**, http://edrn.nci.nih.gov
- **Director's Challenge: Toward a Molecular Classification of Tumors**, http://dc.nci.nih.gov
- **Clinical Proteomics Program,** http://clinicalproteomics.steem.com/index.php
- **Tissue Array Resource Program (TARP)**, http://resre.nci.nih.gov/tarp/
- $ **Mouse Models of Human Cancer Consortium (MMHCC)**, http://emice.nci.nih.gov/
- $ **Specimen Resource Locator**, http://pluto3.nci.nih.gov/tissue/

PATIENT-ORIENTED RESEARCH

Clinical Research

Clinical trials to evaluate improved and novel prevention, detection, and treatment strategies are carried out within the **National Clinical Trials Program in Treatment and Prevention** infrastructure that includes NCI Cancer Centers, Cooperative Groups, SPOREs, the CCOP and minority-based CCOPs. In addition to supporting clinical trials, NCI supports a broad range of clinical research to develop new agents and novel approaches for the prevention, early detection, and treatment of cancer. Programs and initiatives that support clinical research include:

- $ **Cancer Therapy Evaluation Program (CTEP)**, http://ctep.cancer.gov/index.html
- **Cancer Trials Support Unit (CTSU)**, http://www.ctsu.org/
- **Program for the Assessment of Clinical Cancer Test (PACCT)**, http://www.cancerdiagnosis.nci.nih.gov/assessment.
- **Physician Data Query** database, http://www.cancer.gov/clinicaltrials/
- The **Biomedical Imaging Program (BIP)**, http://www3.cancer.gov/dip/
- **In vivo Cellular and Molecular Imaging Center (ICMIC)**, http://www3.cancer.gov/bip/ICMICs.htm
- **Rapid Access to Intervention Development (RAID),** http://dtp.nci.nih.gov/docs/raid/raid_index.html
- **Rapid Access to NCI Discovery Resources (RAND)**, http://dtp.nci.nih.gov/docs/rand/rand_index.html
- **Rapid Access to Prevention Intervention Development (RAPID)**, http://www3.cancer.gov/prevention/rapid/

Cancer Control and Outcomes

NCI supports patient-oriented research that includes intervention, nutrition, chemoprevention, biobehavioral influences on disease, cancer screening, pain and symptom management, quality of life, ethics, confidentiality, and understanding health disparities. A number of initiatives address ways to improve the quality of cancer care and include:

- $ The **Cancer Care Outcomes Research and Surveillance Consortium (CanCORS)**, (lung and colorectal cancer), http://healthservices.cancer.gov/cancors/
- $ The **HMO Cancer Research Network**, http://healthservices.cancer.gov/hmo/
- $ The **Patterns of Care/Quality of Care** initiative, http://healthservices.cancer.gov/surveys/poc/
- $ **SEER-Medicare Linked Database**, http://healthservices.cancer.gov/seermedicare/

ADDRESSING HEALTH DISPARITIES

NCI has identified cancer health disparities as an area of public health emphasis in *The Nation's Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2004*. Disparities are widespread and decentralized, encompassed by the broad scope of research supported by NCI. The challenges are to understand what causes disparity, develop potent interventions, and implement them.

In 2000, NCI established the Center to Reduce Cancer Health Disparities,(http://crchd.nci.nih.gov/, to function as an organizational locus for the critical tasks needed to translate discovery into delivery. NCI supports a number of partnerships, collaborations, initiatives, and programs that focus on reducing cancer health disparities. For example, Partnerships between NCI, the Centers for Disease Control and Prevention (CDC), the Health Resources and Services Administration, and other federal and non-federal agencies are working together to develop and improve interventions to increase screening and follow-up for breast, cervical, and colorectal cancers in underserved and historically underscreened women. Other activities include:

- $ The **Special Populations Network**, http://crchd.nci.nih.gov/spn/about/index.html.
- $ **Center for Population Health and Health Disparities,** to begin in 2003, in collaboration with the National Institute of Environmental Health Sciences (NIEHS) National Institute of Aging (NIA), and the National Institutes of Health (NIH) Office of Behavioral and Social Sciences Research.
- $ The **Cooperative Planning Grant for Cancer Disparities Research Partnerships** will support the expansion of radiation oncology clinical trials in three institutions that serve populations of Native Americans, African Americans, Hispanics, and rural Appalachians.
- $ The **California Health Interview Survey (CHIS)**, http://appliedresearch.cancer.gov/surveys/chis/
- $ **Network for Cancer Control Research among Native American/Alaska Native Populations**, http://www.mayo.edu/nativecircle/networkres.html

CANCER INFORMATION AND EDUCATION

NCI provides information about women's health to cancer patients, health and research professionals, and the public in a variety of formats. The most recent, complete, and reliable information is available to assist cancer patients, their families, and their health care providers in making decisions about cancer prevention, detection, treatment, and follow-up care through NCI's website, http://cancer.gov. This site features LiveHelp, a web-based instant messaging service.

NCI's website links to a gateway to information and education about ongoing research programs and activities through NCI's Cancer Information Service (CIS). Printed publications and audiovisual material are available for a range of cultural and literacy levels and can be accessed directly via http://cis.nci.nih.gov or toll-free number, 800-4-CANCER. Through its Partnership Program, the CIS provides technical assistance and materials to aid local, regional, and state partner organizations to reach and educate minority and medically underserved women with limited access to health and cancer information. In 2002, the CIS, partnering with local organizations, completed four "digital divide" projects, whose goal was to increase information technology use for cancer information among underserved population.

NCI disseminates information through press releases and television, supplemented with in-depth background information through the BenchMarks website and accessible via http://cancer.gov. 2002 BenchMarks issues featured the results of the Women's Health Initiative study on postmenopausal hormone use, August 2002; and cervical cancer screening, April 2002.

NCI's Office of Education and Special Initiatives (OESI) has developed the Clinical Trials Education Series, a group of mixed media about participating in cancer clinical trials. The series includes workbooks, booklets, brochures, videos, slide programs, and a web-based course. The OESI has also developed the Facing Forward Survivor Series, publications about the issues that survivors face after treatment. This series includes Spanish language adaptations.

The *Cancer Progress Report 2001*, http://progressreport.cancer.gov, is the first in a new series of NCI reports to describe the Nation's research progress against cancer through research and related efforts. The report is based on

the most recent data from NCI, the CDC, other federal agencies, professional groups, and cancer researchers. The *Report* was designed to help policymakers review past efforts and plan future ones; to help the public better understand the nature and results of strategies to fight cancer; and to inform researchers, clinicians, and public health providers of the research gaps and opportunities that will pave the way for future progress.

BREAST CANCER

Despite significant advances in detection, diagnosis, treatment, and prevention, breast cancer continues to have a devastating impact on American women. By the end of 2003, an estimated 211,300 women are expected to be diagnosed with breast cancer and nearly 39,800 will die of the disease. An estimated 2 million women in the United States have either survived breast cancer or are living with breast cancer today.

SEER data indicate that breast cancer is responsible for the highest number of new, invasive cancer cases among women each year and, after lung cancer, the second leading cause of cancer deaths in women. The increase in breast cancer incidence that began in the early 1980s continues today, although this increase has slowed dramatically since 1987. Despite this improvement, recent years have shown an increased incidence in women over the age of 50. Overall, breast cancer mortality rates also have shown an encouraging downward trend, dropping 1.4 percent per year from 1989 to 1995 and 3.2 percent per year thereafter. This trend suggests that improved breast cancer management, from early detection to treatment, is having a beneficial effect. The largest decrease in mortality occurred in young, white and African-American women. Currently, white women exhibit greater incidence than African American women, but lower mortality rates.

NCI's Breast Cancer Progress Review Group released a report in 1998 that evaluated the current state of breast cancer research, identified research gaps and resource needs, and developed recommendations for future research priorities to move the field ahead. In 2003, an internal working group at NCI will begin a review of the progress of the national breast cancer research program over the last 5 years by looking at disease trends, new FDA-approved interventions; clinical trials, both new and ongoing; advances in scientific knowledge, and NCI-supported research activities.

BIOLOGY AND GENETICS

Molecular Profiling. DNA array technology is being used to establish molecular profiles of gene expression in a series of breast cancer specimens and normal, at-risk, breast. The analysis results in an easily visualized clustering of specimens that have similar patterns of gene expression and provides a relative measure of the similarity of the expression patterns between any two specimens. Identification of clusters of genes that are expressed in different cell types or are associated with cell proliferation have demonstrated that this technology will allow exploration of potentially important interactions between different cell types in tumors.

Mouse Models. NCI sponsors a number of projects such as the MMHCC, to develop, analyze, and apply mouse cancer models. Significant improvements in the technology of modeling human breast cancer in mice have resulted in models that more accurately mimic the human situation in which genetic alterations occur in a subset of somatic cells. Mouse models have facilitated the investigation of distinct pathways involved in breast cancer, important for cancer prevention and therapeutic studies and for target validation in cancer drug discovery http://emice.nci.nih.gov/.

Estrogen Receptors. Estrogens influence the growth, differentiation, and function of the human reproductive system and stimulate the proliferation and metastatic activity of nearly 40 percent of breast tumors. Estrogen receptor (ER) expression seems to correlate with prognosis and may provide targets for therapy. Treatments such as tamoxifen and raloxifene, which block ERs, do not seem to affect ER-negative tumors, found in 20 to 30 percent of all breast tumors and more prevalently in women under age 50, in black women at all ages, and in women at risk due to alterations in the BRCA1 gene. Animal models of ER-negative breast cancer may lead to strategies for preventing ER-negative disease. Other studies are examining possible correlations between tumor cell characteristics, age, race, reproductive status, and lifestyle issues and ER status.

Cyclin E. Cyclin E, a key cell cycle regulator involved in the control of the initiation of both DNA replication and centrosome duplication, is often overexpressed in a variety of malignant tumors, including breast, gastric, and ovarian and appears to correlate with a more aggressive breast cancer phenotype and a poorer patient outcome. Recent studies in cell lines show that cyclin E overexpression leads to chromosomal instability and polyploidy, and

along with patient analyses, suggest that cyclin E expression may be a powerful prognostic indicator for survival for patients with breast cancer.

Gene Mutations. Fifteen to 20 percent of familial breast cancers can be accounted for by germ-line mutations in the breast cancer susceptibility genes BRCA1 and BRCA2. Estimates of the lifetime risk of breast cancer among women with BRCA1 or BRCA2 vary from 56 percent to as high as 80 percent to 85 percent (as opposed to a 12 percent lifetime risk for most women). These women have an increased risk of ovarian cancer as well. Studies in Ashkenazi Jewish women diagnosed with breast cancer, 7 percent of whom carry mutations in BRCA1 and BRCA2, have found that early birth in women with BRCA mutations does not confer protection against later breast cancer. Investigators in NCI's Cancer Genetics Network (CGN), http://epi.grants.cancer.gov/CGN/ are examining whether hormonal factors and genes involved in hormone metabolism, carcinogen metabolism, and DNA repair modify risk for cancer in women who with BRCA1 and 2 mutations.

Rare germ-line mutations in p53 and CHK2 (Li-Fraumeni syndrome), PTEN (Cowden syndrome) and the serine threonine kinase STK11/LKB1 (Peutz-Jegher syndrome) account for another small fraction of the familial cases. Genes for the remaining familial clusters are unknown and may be caused by low-penetrance susceptibility genes. Causes for sporadic cancers are not clear, but many genes that contribute to growth and apoptosis have been found to be deregulated in sporadic breast cancer.

The Cancer Genome Anatomy Project, http://cgap.nci.nih.gov/, coordinates data and reagents that will support advances in molecular detection and diagnosis with the goal of providing a complete picture of all major molecular changes that occur during cancer development. CGAP currently has information on nearly 20,000 cDNA sequences for normal and malignant breast, which include 400 genes unique to breast.

Specimen Resources. NCI Cooperative Breast Cancer Tissue Resource provides researchers with access to approximately 9,000 cases of formalin-fixed, paraffin-embedded breast cancer tissue samples with associated pathology and clinical data, particularly well suited to validation studies of diagnostic and prognostic markers http://www.cbctr.ims.nci.nih.gov.

RISK FACTORS

Genetic Factors. The Breast and Ovarian Cancer Family Registries include information and laboratory specimens from over 6,000 families at risk and support investigations in genetic epidemiology, including the identification and characterization of genes, gene-gene interactions, and gene-environment interactions. http://epi.grants.cancer.gov/BCFR/index.html. The CGN, a group of collaborative clinical centers of excellence in cancer genetics, participate in the development and testing of interventions to better prevent, detect, and treat breast cancer among individuals at high risk http://epi.grants.cancer.gov/.

Diet. It has been hypothesized that estrogen-like compounds in soy foods influence the risk of breast cancer. A population-based case-control study among women in China found that soy food consumption appears to lower the risk of breast cancer. High soy and dietary folate intake during adolescence were associated with reduced risk of breast cancer later in life. This effect appeared to be strengthened by increased dietary intake of methionine, vitamin B_{12}, and vitamin B_6. There is conflicting data on the association between dietary fat and breast cancer risk. Studies are ongoing, although a recent analysis showed no overall association.

Obesity. Before menopause, obese women are at a decreased risk for breast cancer. Post menopause, the same obese women have an increased risk for breast cancer, which is ameliorated by hormone therapy. The roles of caloric intake and energy balance are under investigation. Limited studies in African American women have shown reduced obesity-associated risks for breast cancer. The Four Corners Breast and Endometrial Cancer Study is investigating obesity and weight change effects on breast and endometrial cancer among minority women, while the Black Women's Health Study is focusing on risk factors for breast cancer that include obesity.

Breast Changes. Case-control studies have shown that increased mammographic breast density, atypical hyperplasia, and nonproliferative benign disease increase the risk for breast cancer. Women who have breast fed one or more children have a slightly reduced risk of breast cancer compared with parous women who have not breast fed.

Other Lifestyle Factors. The Health, Eating, Activity, and Lifestyle (HEAL) study, begun in 1996, is designed to explore the associations among physical activity, eating habits, weight patterns, diet, hormones, prognostic factors, and the differences in these associations among various racial and ethnic groups in relation to risk for breast cancer. http://appliedresearch.cancer.gov/surveys/heal/

Diethylstilbestrol (DES). Women given DES during pregnancy showed a modest, but statistically significant increase in breast cancer risk which was not exacerbated by family history, use of oral contraceptives, or hormone therapy. A study of DES-exposed daughters showed a slight, not statistically significant, increase in risk for invasive breast cancer, and also for ER positive tumors in women over 40, but not in younger women.

Hormones. Estrogen , essential for the normal growth and development of the breast and reproductive tissues, childbearing, and regulation of the menstrual cycle may play a role in carcinogenesis. Lifetime exposure to estrogen has been linked to an increased risk for breast cancer. Progestins, acting with estrogen, bring about mammary gland proliferation. The role of progestins in breast cancer etiology has been examined in the context of oral contraceptives and postmenopausal hormone use. Prolactin, a polypeptide hormone, essential for the development of mammary glands and for lactation, enhances the rates at which mammary tumors develop in animals. A population based case-control study of breast cancer in Asian women living in the U.S. found that endogenous hormone levels varied with differences in degree of westernization and that aspects of hormone metabolism may play a role in population differences in breast cancer incidence. Other studies of endogenous sex hormones have shown strong correlations between increased levels and increased risk for breast cancer in postmenopausal women.

Postmenopausal Hormone Use. Recent studies on postmenopausal hormone use and breast cancer have suggested that length of use and the type of postmenopausal hormone therapy, estrogen alone versus an estrogen/progestin combination, may be important factors. A recent reanalysis of data from more than 50 studies on breast cancer showed an increased risk of breast cancer in women who used postmenopausal hormone therapy (estrogen only) for longer than 5 years. Risk increases with the length of hormone use but decreases after a woman stops taking hormones.

After estrogen alone was linked with an increased risk for endometrial cancer, many women began using estrogen/progestin combination therapy. In July 2002, NIH stopped early the Women's Health Initiative multicenter clinical trial of estrogen plus progestin in 16,608 healthy menopausal women who had not had a hysterectomy. Mid-trial results showed adverse health effects, including a 26 percent increase in breast cancer risk (or 8 additional breast cancers per 100,000 women); and a higher risk for developing heart attacks, strokes, and blood clots in the legs and lungs. Although the estrogen plus progestin therapy yielded benefits, including fewer cases of hip fractures and colon cancer, on balance the harm was greater than the benefit. Increased breast cancer risk has not been found in the ongoing study of estrogen-only (in women who already had a hysterectomy before joining the study) http://cancer.gov/clinicaltrials/digest-postmenopausal-hormone-use.

Oral Contraceptives. The Women's Contraceptive and Reproductive Experiences (Women's CARE) study, a population-based, case-control study involving over 9,000 women ages 35-64 found that oral contraceptive use was not associated with a significant increase in risk of breast cancer. A 2002 study concluded that women with BRCA1 mutations who had used oral contraceptives for 5 or more years had a 33 percent increased risk of breast cancer. Those women in the study who used oral contraceptives before the age of 30, who had been diagnosed with breast cancer before age 40, or who used early types of oral contraceptives (before 1975) had a higher risk of breast cancer. Carriers of BRCA2 mutations did not show the increased risk with oral contraceptive use. Other studies have suggested that long-term use of oral contraceptives before first pregnancy increases risk.

Environmental Factors. NCI research programs are investigating the links between breast cancer and exposures to pesticides, air pollution, drinking water contaminants, electromagnetic and ionizing radiation, and lifestyle and other factors. A major thrust of current research work is focused on biomarker approaches (genetic, molecular, cellular, and tissue or organ specific) as one way to assess internal dose. Research is being conducted to measure the estrogenicity of environmental chemical exposures. Markers of exposure are being developed and validated. Current research includes identification of geographic areas with increased breast cancer incidence, morbidity, and mortality and potential contributions of local environmental factors. Of particular concern has been the relationship to risk of organochlorine products, which are established endocrine disrupters. Investigators in the Division of Cancer Epidemiology and Genetics (DCEG) have undertaken several studies in populations uniquely exposed,

including a study in India, where DDT is still used, and in occupational groups such as farmers, dry cleaners, and formaldehyde workers.

The Long Island Breast Cancer Study Project (LIBCSP) is an NCI and NIEHS multistudy effort to investigate whether environmental factors are responsible for breast cancer in specific counties in New York and Connecticut. Scientists have found no evidence supporting an association between organochlorines, including the pesticide DDT, its metabolite DDE and industrial compounds known as PCBs; and heightened risk of breast cancer. Exposure to air-polluting polycyclic aromatic hydrocarbons in the environment appears to elevate women's risk of breast cancer, but women with a higher ratio of 2-hydroxyestrone had decreased risk of breast cancer by a modest 50 percent. Further analyses and a follow-up study are in progress. A case-control study is investigating the possible association between electromagnetic fields and increased risk for breast cancer. Findings from this study are expected in mid- to late 2003. In 2001, NCI completed development of a prototype health-related geographic information system (GIS-H) for Long Island that provides researchers with a new advanced tool to investigate relationships between breast cancer and the environment on Long Island http://epi.grants.cancer.gov/LIBCSP.

Recently, a joint NCI, NIEHS, and CDC task force developed several strategies to address the high breast cancer rates in Marin County, California, including recalculating and comparing breast cancer rates for Marin County and all of California, enhancing existing GIS in California, completing epidemiologic studies on breast cancer in Marin County, and partnering with the CDC to explore opportunities and technologies for measuring environmental exposures.

Radiation. Current research in the Radiation Epidemiology Branch focuses on the specific effects of diagnostic, therapeutic, and occupational exposure to ionizing radiation, a known risk factor for breast cancer, in established cohorts such as X-ray technologists, ataxia-telangiectasia carriers, and A-bomb survivors. Multidisciplinary investigations are focusing on genetic susceptibility to radiation carcinogenesis and the interactions of radiation dose, hormonal factors, and genetic factors. Scientists have found that women with scoliosis (abnormal curvature of the spine) who were exposed to multiple diagnostic X-rays during childhood and adolescence have a 70 percent higher risk of breast cancer than women in general. Nonionizing radiation (electromagnetic-field) exposure has been hypothesized to affect breast cancer risk through changes in melatonin levels that affect estrogen secretion. Current research is measuring electromagnetic-field exposure in several cohorts, including teachers in California, nurses, X-ray technologists, who have the potential for cumulative exposures up to as much as 0.2 Gy, and radiation technologists.

PREVENTION

Chemoprevention. Many breast cancer prevention studies are testing the effectiveness of selective estrogen receptor modulators (SERMs), such as tamoxifen and raloxifene.

One of the largest breast cancer prevention studies ever undertaken, the Study of Tamoxifen and Raloxifene (STAR), has enrolled 15,000 of a planned 19,000 participants through more than 500 centers across the United States, Puerto Rico, and Canada. The study will determine whether the drug raloxifene, which is used for osteoporosis prevention and treatment and previously shown to reduce breast cancer incidence, is as effective as tamoxifen in reducing the risk of breast cancer. The long-term safety of both drugs will be studied. Thirty percent more minority women have joined the study than in the preceding Breast Cancer Prevention Trial of tamoxifen, http://www.cancer.gov/clinicaltrials/digestpage/STAR. The Capital Area SERM Study is evaluating the safety of raloxifene in premenopausal women who are at increased risk for breast cancer.

Women at high risk for breast cancer, especially premenopausal women, who took the drug tamoxifen were less likely to be diagnosed with benign breast conditions, such as atypical hyperplasia, than women at equal risk who took a placebo. The results of the 2001study are part of the follow-up for the Breast Cancer Prevention Trial.

Prophylactic Surgery. Studies published in 1999, found that prophylactic mastectomy was associated with a reduction in incidence of breast cancer of at least 90 percent among women with a family history of the disease. Similarly, other recent studies have found that prophylactic mastectomy, salpingo oophorectomy (removal of the ovaries and fallopian tubes) or oophorectomy (removal of the ovaries) reduced the number of cases of breast cancer in women with alterations in BRCA1 or 2. A study of breast cancer among Swedish women who had breast reduction surgery found that removal of greater amounts of tissue reduced breast cancer risk dramatically.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Imaging Technologies. NCI is funding research on a variety of technologies for breast imaging, including digital mammography, elastography, magnetic resonance imaging (MRI), magnetic resonance spectroscopy, ultrasound techniques, positron emission tomography (PET), single-photon emission computed tomography (SPECT), and thermography. Projects studying PET and SPECT involve the development of imaging agents designed to look at molecular, biological, or metabolic characteristics, such as radiolabeled estrogen-like compounds to indicate the overexpression or location of estrogen receptors. Optical-imaging techniques provide information about the presence and amount of various chemicals in tissue. Optical technologies using the near-infrared region of the spectrum, combined with MRI, may allow sensitive and specific detection of breast abnormalities. Thermography (digital infrared imaging) can detect the increase in regional breast temperature resulting from increased chemical and blood vessel activity in both precancerous tissue and the area surrounding a developing breast cancer.

Mammography NCI is funding research to reduce the already low radiation dosage of mammography; enhance mammogram image quality; develop statistical techniques for computer-assisted interpretation of images; enable long-distance, electronic image transmission technology (telemammography/teleradiology) for clinical consultations; and improve image-guided techniques to assist with breast biopsies. Computer-enhanced images in digital mammography can detect suspicious areas that human review might miss. In 2001, NCI and the American College of Radiology Imaging Network launched the Digital Mammographic Imaging Screening Trial (DMIST) to compare digital mammography to standard film mammography, http://www.dmist.org.

MRI. Several large studies are examining the application of MRI in the detection of breast cancer to reduce the number of false-positive X-ray mammograms that lead to biopsy. MRI in combination with near-infrared optical imaging is being evaluated for heightened sensitivity and specificity in breast abnormality detection.

Other Imaging Initiatives Ongoing studies of the NCI-supported American College of Radiology Imaging Network, include a study of breast MRI to assess response to chemotherapy prior to surgery and a study partially supported by the Avon cosmetics company to study ultrasound for screening. The Small Animal Imaging Resource Program supports studies to develop and apply a wide variety of functional, quantitative imaging modalities through partnerships with industry, http://www3.cancer.gov/dip/sairp_abs.htm .

Gene Expression Profiles. Studies in the Director's Challenge program, http://dc.nci.nih.gov, have distinguished five subsets of breast cancers, previously unidentified by morphology. Two of the subsets, HER2/neu overexpressing and basal cell tumors, correspond to poor prognosis.

Population-Based Breast Screening. The Breast Cancer Surveillance Consortium works to reduce breast cancer mortality by enhancing current understanding of breast cancer-screening practices and fostering collaborative research in the hope of improving the practice of community-based mammography screening, http://breastscreening.cancer.gov/ .

The International Breast Cancer Screening Network (IBSN), a consortium of 25 countries that have active population-based screening mammography programs, is dedicated to collaborative research aimed at identifying and fostering efficient and effective approaches to breast cancer control worldwide through population-based screening mammography, http://appliedresearch.cancer.gov/ibsn/.

NCI, in partnership with the Centers for Medicare and Medicaid Services, the National Asian Women's Health Organization, the CIS, and Asian community organization, recently released educational brochures in English, Chinese, Vietnamese, and Tagalog, to encourage Asian-American/Pacific Islander women in their 40s and older to get mammograms every 1 to 2 years using Medicare benefits for screening.

Sentinel Node Biopsy. The status of lymph node involvement is likely to gain increased clinical significance in the future as improved imaging techniques detect growing numbers of women who have small tumors. NCI is sponsoring two large trials comparing long-term survival for patients assessed using the less invasive technique of sentinel node biopsy with those having complete axillary lymph node dissection, which has a number of associated serious, long term side effects. The studies will also compare the postsurgical side effects between the two groups.

TREATMENT

Proteomics. A new clinical proteomics program investigates new methods to diagnose cancer earlier and monitor the protein status of a patient before, during, and after treatment for cancer by generating a protein "fingerprint" Potential benefits include developing individualized therapies using targeted treatments; preclinical assessment of the toxic and beneficial effects of treatments; earlier diagnosis; and improving the understanding of tumors at the protein level to develop more effective treatments.

Adjuvant Therapy

Tamoxifen. In the October 2002, investigators with the National Surgical Adjuvant Breast and Bowel Project (NSABP) reported that women with very small breast tumors who received both radiation therapy and the drug tamoxifen after surgery had fewer recurrences of cancer in the same breast than women who received either radiation therapy or tamoxifen, but not both. This supports treating most women with early breast cancers with radiation therapy following conservative surgery. Additionally, women with ER-positive tumors benefit from tamoxifen treatment, suggesting that tumor size as well as tumor type, hormone sensitivity, and the woman's general health need to be considered when making treatment decisions.

Fulvestrant. The drug tamoxifen is effective against breast cancer by binding to estrogen receptors, but not in all tumors and for a limited time in others. High levels of the proteins, HER-2 and AIB1 in combination, seem to make tumors in some women more resistant to tamoxifen. Fulvestrant, effective against tamoxifen-resistant tumors, attaches to the ER but, unlike tamoxifen, destroys the receptor, thereby blocking all estrogen activity. The FDA recently approved fulvestrant for treatment of tamoxifen-resistant, ER-positive breast cancers. Fulvestrant was recently shown to be as effective as anastrozole, an aromatase inhibitor, in treating postmenopausal women with advanced, previously treated breast cancers. It is not yet known whether fulvestrant is effective in premenopausal women.

Aromatase Inhibitors. A new class of drugs, aromatase inhibitors (AIs), have been shown to be effective in treating advanced, ER and progesterone receptor positive breast cancer, and also show promise as adjuvant therapy for early breast cancer. The FDA has approved anastrozole (Arimidex®) for adjuvant treatment of breast cancer based on the results of the Arimidex, Tamoxifen, Alone or in Combination trial of early breast cancer, which compared 5 years of treatment with tamoxifen alone, anastrozole alone, or the two drugs together, after initial surgery. Anastrozole has been shown to be as effective as tamoxifen as a first-line treatment for advanced breast cancer, extending length of time to disease progression, with fewer side effects. Another AI, letrozole (Femara®), has also received FDA approval for treatment of postmenopausal women with hormone-sensitive advanced breast cancer.

Combination Therapy. PACCT has developed a trial to identify patients with low-risk and early-stage disease who will not benefit from systemic adjuvant chemotherapy. Intermediate and high-risk participants with node-negative, hormone receptor-positive tumors between 1 to 3 cm will be treated with endocrine therapy plus or minus systemic chemotherapy.

"Dose Dense" Chemotherapy. Commonly used drugs in breast cancer treatment when administered under a dose dense regime, with increased frequency and the addition of filgrastim to prevent neutropenia showed decreased disease recurrence and significant survival benefits for patients in a study of node-positive women. Side effects were not found to be more severe in the dose dense groups.

Herceptin®. Trastuzumab (Herceptin®) with standard chemotherapy, shown to be effective for the treatment of metastatic breast tumors that overexpress the *HER2/neu* protein, is now being studied in earlier stages of breast cancer. Several new Phase 3 clinical trials, which should have results in 2006 or 2007, are testing the addition of Herceptin® to the postsurgery treatment of earlier stage breast cancer with standard chemotherapy agents (Adriamycin® and Cytoxan®) and Taxol®. Herceptin's® effect on the heart is being assessed, since earlier studies suggested that it could cause problems in some women.

High-Dose Chemotherapy with Stem Cell Transplant. The final analysis of data from one of the major U.S. trials of high-dose chemotherapy with stem cell transplant for breast cancer shows that it holds no survival advantage over intermediate-dose therapy. Early results from two other trials add to the growing evidence that high-dose regimens do not increase breast cancer survival. Several large, randomized trials are still ongoing. The current recommendation is that women should receive high-dose chemotherapy with transplant only as part of a high-priority clinical trial so that they can be followed for several years after treatment.

Effectiveness of Shorter Radiation Treatment. Results of a new study among node-negative lumpectomy treated women shows that reducing daily radiation therapy from 5 weeks to 3 weeks is equally effective in preventing cancer recurrence. Shortened radiation schedules lessen the overall burden for these patients in terms of personal costs, travel, and time off work, and for the health care system by reducing costs and freeing resources for use by more patients. The results of the study can only be applied to the subgroup of women in the trial.

Effectiveness of Lumpectomy Compared to Mastectomy. Two longitudinal studies, one initiated in the 70's and the other in the 80's report that women with early breast cancers, treated with breast-conserving surgery plus radiation therapy were as likely to be alive and disease-free 20 years later as women treated with mastectomy.

Other Research. Other ongoing therapeutic research includes studies of gene therapy strategies that target key stages of the cell cycle such as programmed cell death by using adenoviral vectors to transfer specific genes; use of angiogenesis inhibitors; chemoprotection by making drug resistant bone marrow cells to reduce potential bone marrow toxicities; immunotherapies designed to stimulate antitumor responses; and complementary and alternative medicine.

CANCER CONTROL, SURVIVORSHIP, AND OUTCOMES RESEARCH

NCI's Office of Cancer Survivorship (OCS), http://dccps.nci.nih.gov/ocs/healthdisp.html, conducts and supports research that both examines and addresses the long- and short-term physical, psychological, social, and economic effects of cancer and its treatment among survivors of cancer and their families. For example, we know that patients exposed to systemic chemotherapy are at increased risk for problems with cognitive functioning (e.g., memory, concentration, executive capacity) and some may be genetically more susceptible to this chronic effect of treatment.

Treatment Decisions. NCI's Office of Education and Special Initiatives and NCI's Office of Women's Health have partnered with the National Center for Policy Research for Women and Families, the Agency for Health Research Quality, the Office of Women's Health, Department of Health of Human Services, and the Office of Research on Women's Health, NIH, to develop education and communication materials to assist women with early-stage breast cancers and their health care providers to make informed treatment decisions. Information provided, will describe the standard surgical options of mastectomy and lumpectomy plus radiation, and the factors that can be considered when making treatment choices.

The OCS supports development of tailored print and interactive health communications, such as the Comprehensive Health Enhancement Support System, which provides a computer-based system of integrated services designed to help individuals cope with a health crisis or medical concern. This system has resulted in several important outcomes, including reduced hospital days.

Pain, Depression, and Fatigue. These were the focus of a July 2002 NIH State of the Science meeting, Symptom Management in Cancer, examining the current state of knowledge on the management of pain, depression, and fatigue in individuals with cancer, and identified directions for future research. The final statement of the conference is available at http://consensus.nih.gov/ta/022/022_intro.htm.

Health Disparities and Cancer Survivors. NCI is supporting projects, 3 of which are on breast cancer, in Cancer Centers to promote research in cancer survivorship among minorities and underserved populations in their communities after the completion of initial treatment, and/or the families of such patients; to strengthen linkages between researchers and community representatives; and to disseminate research findings to targeted community and members of the Cancer Center. NCI is also funding projects on issues such as menopausal symptom relief in breast cancer patients, breast cancer and function in aging women, and quality of life in long-term cancer survivors.

CERVICAL CANCER

An estimated 12,200 cases of invasive cervical cancer are expected to be diagnosed in American women in 2003, with about 4,100 deaths from the disease. The overall incidence and mortality rates in the United States have declined by approximately 80 percent, since 1950. This dramatic decrease is largely due to screening programs using the Papanicolaou test (Pap smear), implemented in the last 50 years. Throughout the world, the incidence of cervical cancer is second only to breast cancer as the leading, invasive cancer among women, although in some

developing nations, cervical cancer is more prevalent. The 471,000 new cases diagnosed annually worldwide are predominantly among the economically disadvantaged in both developing and industrialized nations.

Women in America have not benefitted equally from the overall cervical cancer mortality reductions noted above. African American women have more than twice the death rate compared with white women. Native Americans of the northern plains; Native Alaskans; and Vietnamese, Korean, and Hispanic women have higher than average cervical cancer mortality rates. Also of note, the incidence rate among Hispanic women declined by 4.3 percent per year between 1992 and 1999, though this rate remains higher than average. Many factors may interact to create and perpetuate discrepancies, including biology, sociocultural factors, economics, and provider issues.

NCI Center to Reduce Cancer Health Disparities (CRCHD) held a series of three meetings in 2001and 2002 on cervical cancer disparities in the United States. The first two meetings examined in detail the geographic patterns of cervical cancer mortality in the United States and explored social, cultural, and system barriers that could be contributing to the disparities in the United States. A working hypothesis was developed of cervical cancer as an index disease that highlights the complex health care issues facing women in the Deep South and Appalachia, regions which also have high rates of other life-threatening, chronic illnesses, as well as chronic living conditions of poverty. The third meeting in October 2002 brought together health care leaders from these regions to address what is known about cervical cancer rates, the health care available to medically underserved women who live there, and information, access, and cultural issues affecting that care. Using currently available research and medical information, participants are developing recommendations in the areas of Communication and Education, Advocacy and Partnerships, Outreach and Services, and Research. Regional and race-specific programs to study cervical cancer disparities are supported through the CRCHD's Special Populations Network.

The *Report of the Gynecologic Cancers Progress Review Group* in 2001 described research priorities and the resources needed to bridge gaps in understanding and overcoming barriers to progress. The PRG stressed the importance of developing an effective prophylactic and therapeutic human papillomavirus (HPV) vaccine, which could have the potential to nearly eradicate cervical cancer globally and also reduce the cost of screening. Additional recommendations specific to cervical cancer included developing better screening and prevention strategies, developing treatment approaches to reduce sexual dysfunction and improved fertility outcomes, and understanding the mechanisms and efficacy of combination therapies. High-impact priorities of the PRG applicable to all gynecologic cancers included a Virtual Shared Specimen Resource (VSSR) and research to understand and improve quality of life and reduce or eliminate disparities related to care. The report is available at http://prg.nci.nih.gov/gyno/finalreport.html.

RISK FACTORS

HPV. Studies have shown that approximately 90 percent of cervical cancers and cervical hyperplasias are associated with HPV, primarily types 16, 18, 31, and 45. HPV type 16 is found in 50 percent of cancers and their precursors, high-grade squamous intraepithelial lesions and various degrees of association with the development of cervical neoplasias. A case-control study of Costa Rican women less than 50 years old found that cervical inflammation may be associated with high-grade lesions and may be an etiologic cofactor in women infected with oncogenic HPV, suggesting that HPV infection is a primary cause of cervical neoplasia and supporting the clinical applications of HPV DNA testing and primary prevention of cervical cancer by vaccination.

Cofactors. Women who have never had a Pap test or who have not had one for several years have a 3- to 10-fold increased risk of developing cervical cancer compared to women who have been tested. Women who first had sexual intercourse at an early age or who have had many sexual partners have a higher-than-average risk of developing cervical cancer due to the risk of infection with HPV. Oral contraceptive use was associated with HSIL/CA among women with fewer than three pregnancies. Another cofactor for cervical cancer, herpes simplex virus-2 (HSV-2) was identified following meta-analysis of seven case-controlled studies.

Investigators are looking at the interactions between immune system functioning, smoking, nutritional and hormonal factors, and the presence of other sexually transmitted diseases in a large study of cervical cancer cofactors. New diagnostic technologies are also being evaluated.

Tobacco. Studies show an increased amount of tobacco-specific cancer-causing agents in the cervical lining of smokers. Active cigarette smokers have been shown to have a two-fold greater risk of developing cervical cancer.

The risk appears to be dose-dependent with women who smoked approximately 20 cigarettes per day associated with high-grade disease. Nonsmokers exposed to environmental tobacco smoke lasting for at least 3 hours per day have 3 times the risk over unexposed nonsmokers. Risk for HSIL or cancer in HPV-positive women increased with the number of live births and was almost three times greater among women who smoked more than six cigarettes a day. Current use of barrier contraceptives reduced the risk. Increased incidence of squamous carcinomas has been associated with smoking, with an inverse risk association for adenocarcinoma.

HIV. The Centers for Disease Control and Prevention (CDC) has designated invasive cervical cancer as an AIDS-defining cancer. 63 percent of HIV-infected women in a study of the Women's Interagency HIV Study (WIHS) were HPV antibody positive at last screen compared to 28 percent of HIV-uninfected women. An association has been found between low amounts of serum retinol and risk of cervical dysplasia in HIV-infected women but not in high-risk uninfected women. HIV-infected women were nearly twice as likely to have high-risk subtypes of HPV infection and had higher rates of high-grade squamous intraepithelial lesions. Anal HPV infection was more common than cervical HPV infection in both HIV-infected and -uninfected women. It is still unclear whether treatment by highly active antiviral therapy for HIV leads to real regression of HPV-associated ano-genital lesions.

Diethylstilbestrol. The drug diethylstilbestrol, given to pregnant women in the United States and Europe between 1938 and the early 1970s to prevent miscarriage or premature delivery, has been linked to the development of clear cell adenocarcinoma, a rare cancer of the vagina and cervix. A study of exposed daughters followed for diagnosis of high-grade disease showed a two to three-fold increase in risk, depending on timing of exposure. Results of the NCI DES Follow-up Study, which has been following over 15,000 exposed men and women since 1992, are anticipated in Spring of 2003.

NCI has partnered with the CDC since 1999 to build a national education campaign on the potential health effects of DES exposure. Information in various formats was developed and tested for a broad range of health care professionals and consumers with and without known DES exposure. The CDC will begin information dissemination in early 2003, including the DES website, http://www.cdc.gov/des/ , and will also convene five teleconferences on topics pertinent to known-exposed persons.

PREVENTION

HPV Vaccine. Several candidate vaccines have undergone preclinical evaluation, and a small number have been approved for clinical trials. One of these vaccines developed at NCI, HPV-16 L1 VLP (virus-like particle), was shown to be safe and effective at stimulating production of HPV antibodies in a Phase 1 trial. A larger scale, double-blind, placebo-controlled efficacy trial of this vaccine was conducted in nearly 2,400 women. All of the women treated with a full course of the vaccine were free of HPV-16 at the end of the trial, while in those treated with a placebo, 41 developed persistent HPV-16 infections, of which 9 progressed to HPV-16-related cervical intraepithelial neoplasia. NCI plans to do a large efficacy trial in Costa Rica involving 10,000 to 15,000 women. Two additional NCI-supported trials were conducted for another VLP vaccine, HPV-16 E7 VLP and a recombinant vaccinia virus containing HPV-16/18 E6 and E7 (TA-HPV). Phase 1 has been completed for HPV-16 E7 VLP, and Phases 1 and 2 are completed for HPV-16/18 E6 and E7.

Diet. Previous research has shown decreased risk of cervical cancer development with dietary intake of beta-carotene and vitamin A. NCI is supporting continued research in this area.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Pap Test Screening. Data from the 1994 National Health Interview Survey show that about one fifth of women ages 18–64 had not had a Pap test in the preceding 3 years, and about half of women with newly diagnosed invasive cervical cancer had not had a Pap test in the past 5 years. The largest groups of unscreened populations include the uninsured; ethnic minorities, especially Hispanics; elderly African-American women; and poor women, particularly those in rural areas; and older women, who do not see it as a risk. NCI has initiated an information dissemination project to improve screening in women over age 65, alerting them to their need for Pap smears. Collaborative research is also underway to find a more accessible and cost effective alternative to Pap tests.

Certain Asian and Hispanic/Latina and Southeast Asian women have greater risk than white women for cervical cancer, while mortality rates are highest among African American women. Low screening rates could account for these trends. Ongoing studies in the Applied Cancer Screening Research Branch, http://dccps.nci.nih.gov/acsrb/ ,

include novel methods to target the older population as well as ethnic and racial minorities for cervical cancer screening. An NCI-supported study among Chinese Americans in the Seattle area resulted in an increase in cervical cancer screening when culturally and linguistically appropriate educational materials were developed, distributed, and followed up with home visits.

The American Cancer Society (ACS) and the U.S. Preventive Services Task Force, in partnership with NCI, have recently published new guidelines for cervical cancer screening, http://cancer.gov/newscenter/pressreleases/cervicalscreen . The guidelines recommend cervical screens 3 years after sexual intercourse is initiated or by age 21, to be repeated every 3 years through age 65 - 70. Women should consult medical advice for screening initiation, frequency, and termination, especially if they are at an increased risk for cervical cancer.

The 2001 Bethesda System, http://cancer.gov/newscenter/bethesda2001 , developed by an NCI-sponsored workshop, is used by the majority of diagnostic laboratories in the United States. It serves as the basis for guidelines for communicating cervical cancer screening results to physicians, published by The American Society for Colposcopy and Cervical Pathology (ASCCP) in 2002.

HPV Testing. An NCI-supported study in Costa Rica indicated that testing for HPV DNA can accurately identify many precancerous changes in the cervix and may be a useful screening tool for cervical cancer in some populations. The HPV test was more sensitive but less specific than conventional Pap testing.

The ASCUS/LSIL Triage Study (ALTS), sponsored by NCI, was designed to help physicians and women decide what to do about ASCUS and LSIL Pap test results. HPV testing followed by ASCUS results proved to be highly sensitive in detecting lesions needing immediate attention. However, HPV testing in women with LSIL is limited because of the high prevalence (82.9 percent) of HPV infection in these women. It was concluded that testing for HPV DNA in women with ASCUS is a more sensitive and specific detector for cervical intraepithelial neoplasia grade 3 (CIN3) or above, compared to a single additional cytologic test. These studies were the partial basis for the ACS/NCI guidelines published in 2002.

Studies of HPV and cervical cancer found that increased viral loads were positively associated with greater risk of an abnormal Pap test within 5 years. Other studies in HPV-positive women were assessed for viral clearance and cytologic regression by HPV DNA testing and thin-layer cytology for 2 years. HPV DNA detection persisted longer than related cytologic abnormalities. It appears that the natural history of HPV can be detected before and after cytologic abnormalities by a more sensitive HPV DNA method.

TREATMENT

Five large randomized clinical trials found that chemotherapy administered with radiation therapy decreased the risk of death from cervical cancer by 30 to 50 percent, supporting concomitant chemotherapy with radiotherapy for advanced disease. There are currently 29 new or ongoing treatment clinical trials, with most investigating the differences between types and combinations of chemotherapy drugs for the treatment of cervical cancer.

CANCER CONTROL, SURVIVORSHIP, AND OUTCOMES RESEARCH

Psychological Issues. The Cognitive Behavioral Stress Management (CBSM) study is exploring the impact of group-based interventions for distress, quality of life, and cervical cellular atypia level. Another study is looking at behavioral and immunologic components that correlate to psychological distress and coping in women diagnosed with mild dysplasia of the cervix caused by HPV infection.

Sexuality Issues. Several studies are under way to track the sexual function and general quality of life for women receiving treatment for different stages of cervical cancer.

Treatment-Related Side Effects. Studies in progress are examining the efficacy of drugs to alleviate or prevent side effects of cervical cancer treatment, including treatment-induced anemia and quality of life changes.

OVARIAN CANCER

In 2003, approximately 25,400 women in the United States are expected to be diagnosed with ovarian cancer, and approximately 14,300 are expected to die of the disease. Incidence rates decreased by 0.7 percent per year between 1989 and 1999. Ovarian cancer is responsible for the highest mortality rates of all gynecologic cancers. Incidence and mortality rates are highest in white women compared to other racial and ethnic groups.

When detected early, ovarian cancer is highly treatable, with a 5-year survival rate of 95 percent. Ovarian cancer is often asymptomatic in its early stages, and symptoms that do occur are often not of the type that would alert most women or their health care providers. Thus, most diagnoses occur at advanced stages of disease, when survival rates are 81 percent for regionally advanced stages and 31 percent for stages with distant metastases.

The *Report of the Gynecologic Cancers Progress Review Group* in 2001 described research priorities and the resources needed to bridge gaps in understanding and overcoming barriers to progress. Recommendations specific to ovarian cancer included: early detection and prevention strategy development, proteomic technology development, elucidation of mechanisms of tumorigenesis and metastasis, as well as clinical trial optimization for new agents, and surrogate markers. The PRG deemed a VSSR essential for all three gynecologic cancers for the support of studies in cancer biology, identification of genetic and molecular signature, specific molecular pathways, and surrogate biomarkers in precursor lesions, metastatic, and recurrent tumors. The PRG also designated research in quality of life issues and disparity reduction and elimination as a high-impact priority for gynecologic cancers. The report is available at http://prg.nci.nih.gov/gyno/finalreport.html.

RISK FACTORS

The lifetime risk of ovarian cancer is 1.8 percent, and its annual incidence is about 61.8 per 100,000 women who reach ages 75-79. The causes of ovarian cancer are unclear. One theory suggests that constant, uninterrupted ovulation increases the risk of ovarian cancer. This could explain why pregnancy, breast-feeding, and oral contraceptive use are associated with a decreased risk of ovarian cancer. Other theories speculate that increased pituitary gonadotropin levels contribute to an increased risk of the disease or that alterations in ovarian blood flow or the transtubal transportation of carcinogens may be involved in the initiation of ovarian cancers.

Exogenous Hormones. Follow up after 20 years of participants in the Breast Cancer Detection Demonstration Project who used estrogen-only menopausal hormone therapy showed a significantly greater risk, dependent on duration of use, for developing ovarian cancer. Women on estrogen-progestin hormone therapy did not demonstrate a change in risk, but this arm of the study was a small sample size and therapy was of relatively short duration.

Inherited Risk Factors. Three inherited ovarian cancer susceptibility syndromes have been described: (1) familial site-specific ovarian cancer, (2) familial breast/ovarian cancer, and (3) Lynch II syndrome (combination of breast, ovarian, endometrial, gastrointestinal, and genitourinary cancers). It is believed that 5–10 percent of ovarian cancers are caused by inherited mutations in the *BRCA1* or *BRCA2* genes.

BRCA1 and BRCA2 Mutations. There are large variations in risk for ovarian cancer in carriers of BRCA1 mutations, indicating that other factors play a role. Recent NCI-funded studies have found that the risk for developing ovarian cancer increases to between 16and 60 percent with a BRCA1 mutation and between 15 and 25 percent with a BRCA2 mutation. Despite these risks for developing ovarian cancer, patients with BRCA mutations were found to survive 20 months longer than patients without the mutation, possibly caused by differences in disease pattern due to the mutation, rather than early detection.

Registries. A Family Registry for Ovarian Cancer (FROC) is being established using histories of families that are positive and negative for ovarian cancer. The variables of interest include race/ethnicity, invasiveness and type of tumor, age at diagnosis, and BRCA1 prevalence. The Breast and Ovarian Family Cancer Registry collected information and specimens from over 6,000 families with the diseases, potentially valuable in the study of the cooperative effects between genetics, the environment, and lifestyle, http://epi.grants.cancer.gov/BCFR/index.html.

Diet. Analyses of questionnaires from women, enrolled in the Nurses' Health Study (NHS) showed a link between ovarian cancer and frequent egg consumption, but no change in risk with antioxidant vitamin consumption from foods or foods and supplements. Women who consumed 2.5 servings of fruits and vegetables per day during adolescence decreased ovarian carcinoma risk by 46 percent, suggesting that antioxidant vitamins are protective when consumed earlier in life.

Genetic Polymorphisms. Scientists supported by NCI are investigating the effects of polymorphisms in genes regulating steroid metabolism, catecholestrogen formation, and detoxification of oxidative damage. A study with population-based controls found that deficiencies in a metabolic enzyme that cause galactose to accumulate in the ovary were not related to ovarian cancer development.

Other Risk Factors. A multicentered, nested case-control study found a direct relationship between circulating levels of IGF-I and an inverse relationship between BMI and risk for ovarian cancer. A different study found a decreased risk with cigarette smoking, alcohol consumption, and complex carbohydrates; and increased risk with upper body obesity, inactivity, and higher intake of fat.

PREVENTION

Oral Contraceptives. Previous studies have shown that the risk of ovarian cancer is decreased by 40 to 50 percent in women who take oral contraceptives, regardless of whether they had children, a family history of ovarian cancer, or hereditary ovarian cancer syndrome. This effect increases with time, ranging from a 10 to 12 percent decrease in risk after 1 year of use to a 50 percent decrease after 5 years and persisting for 10–15 years after use is discontinued. A study in 840 Israeli women found that additional births were protective in BRCA1/2 mutation carriers; however, only noncarriers had decreased risk with oral contraceptive use.

Fertility Drugs. Women who had never given birth, or had used fertility drugs, even when used for over 12 months, were not at increased risk for ovarian cancer. Increased risks were associated with endometriosis and other unknown causes of infertility. An NCI-funded study is examining medical records of women in Denmark who have received ovulation-stimulating drugs to identify medical conditions that may increase risk of ovarian cancer.

Prophylactic Oophorectomy. Oophorectomy after childbearing in BRCA1/2 mutation carriers decreased risk of ovarian cancer by 96 percent. Side effects of premature menopause are treated medically, and with diet and exercise, but there is little data on risks of premature menopause. NCI Gynecological Oncology Group and CGN are collaborating on a national, prospective follow-up study that will investigate precursor lesions, incidence of cancer prior to ovary removal, and effects on quality of life. Women who don't have surgery will be monitored using a novel CA-125 measure that follows levels over time to assess alterations in the ovaries.

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Proteomics. The FDA/NCI Clinical Proteomics Program, in collaboration with Correlogic Systems Inc., have developed a procedure to distinguish patterns of protein expression in blood samples from unaffected women and those with ovarian cancer. A blinded set of test samples correctly identified 50 of 50 bloods from women with cancer and 63 of 66 samples from unaffected women. This technology was able to recognize a cancer signature in the blood of all stage I ovarian cancer cases, albeit in a small sample size. A pilot diagnostic study is following women currently in ovarian cancer remission and archiving serial samples of blood through relapse or continued remission from which to identify changes in proteomic profiles that are indicative of disease recurrence and to compare these results against the results of the existing marker, CA-125. Trials are under way at NCI to evaluate proteomics both alone and in combination with current screening methods for ovarian cancer.

Gene Expression Profiles. Studies in the Director's Challenge program, http://dc.nci.nih.gov/, have developed profiles in ovarian cancer cells that can distinguish between morphologic subtypes, high- verus low-grade tumors, and alterations in BRCA1 and BRCA2.

Microarray Technology. Scientists participating in NCI investigator-initiated research have been testing the feasibility of a cDNA microarray technology to identify the overexpression of the biomarker osteopontin. The technology found significant differences between healthy and cancerous cells, tissue and plasma, evidencing an association between osteopontin and ovarian cancer.

Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) Trial. Screening for ovarian cancers, one component of the PLCO trial, includes a physical examination of the ovaries, a blood test for the tumor marker CA-125, and transvaginal ultrasound in healthy women, ages 55–74, http://dcp.nci.nih.gov/plco.

3D Power Doppler Ultrasound. In a comparison with two-dimensional (2D) imaging, 3D Doppler Ultrasound both allowed for correct identification of all malignancies. Specificity and positive predictive value improved with 3D use, indicating the possibility of clinical advantages for detection.

National Ovarian Cancer Early Detection Program. The program is assessing the detection of precancerous lesions and early changes of the ovaries using a less invasive in-office laparoscopy technique for ovary visualization and tissue sample collection, the "ovarian pap test." The program is currently enrolling 6,000 high-risk, asymptomatic women and women with confirmed or suspected ovarian cancer.

Cancer Genome Anatomy Project. Molecular markers for the detection of ovarian cancer are a high priority of this gene discovery effort. Ovarian cDNA sequences in the CGAP database now number more than 300,000. These sequencing efforts have identified two known unique ovarian-specific sequences and nearly 1,000 unknown ovarian-unique sequences.

TREATMENT

New Drug Strategies. The use of drug combinations holds promise in overcoming the resistance to platinum-based drugs that develop in many ovarian cancers after initial treatment. The drugs oxaliplatin, epirubicin, liposomal doxorubicin, topotecan, oral etoposide, gemcitabine, and vinorelbine have produced responses in ovarian cancer patients when used alone and are now being tested in two- and three-drug combinations. Also promising in early studies, is the use of a second, or consolidation round of standard-dose chemotherapy for patients whose tumors have responded well to the first round. Data from two large trials has indicated that intraperitoneal therapy may have more side effects but may offer some disease-free and overall survival advantages over intravenous therapy for selected patient populations. Innovative approaches to the treatment of advanced ovarian cancer in development or in early trials include therapeutic vaccines, gene therapy, and antiangiogenic agents.

ENDOMETRIAL CANCER

Cancer of the corpus uteri, or endometrium, is the fourth most common invasive cancer among women in the United States. An estimated 40,100 American women will be diagnosed with uterine cancer in 2003, and approximately 6,800 will die from the disease. The incidence of endometrial cancer declined during the 1970s and 1980s; however, from 1988 to 1999 there has been an 0.6 percent increase per year. Average incidence rates for white women were 26 per 100,000 from 1992 to 1999, while African American incidence rates were significantly less at 17.7 per 100,000. Average mortality rates are opposite, with the mortality rate for white women at 3.9 per 100,000 and mortality rates for African Americans nearly double that at 7.0 per 100,000.

The *Report of the Gynecologic Cancers Progress Review* Group in 2001 described research priorities and the resources needed to bridge gaps in understanding and overcoming barriers to progress. Recommendations specific to endometrial cancer included: developing animal models and imaging methods, and conducting clinical studies for detection and prevention. The PRG identified a VSSR as essential to all of the gynecological cancers for support of studies in cancer biology, identification of genetic and molecular signature, specific molecular pathways, and surrogate biomarkers in percursor lesions, metastatic, and recurrent tumors. The PRG also designated research in quality of life issues and disparity reduction and elimination as high-impact priorities for gynecologic cancers. The report is available at http://prg.nci.nih.gov/gyno/finalreport.html.

BIOLOGY

The Cancer Genome Anatomy Project (CGAP). CGAP currently includes about 84,000 cDNA sequences of normal endometrium and malignant endometrial tumors with 3 known and 3,857 unknown unique genes.

Microsatellite Instability (MSI). Approximately 20 percent of endometrial cancers demonstrate MSI, which is the abnormal expansion or contraction of small repetitive DNA sequences due to defects in the DNA mismatch repair pathway. MSI is a common feature of hereditary nonpolyposis colorectal cancer (HNPCC). Among HNPCC families, endometrial cancers are the second most common tumors. In hereditary cases of endometrial cancer, mutation of the MSH2 or MLH1 mismatch repair gene is causative of HNPCC and the MSI phenotype. However, most endometrial cancers with MSI are the result of somatic inactivation of the hMLH1 gene by promoter

hypermethylation. Findings of recent studies are helping scientists understand the initiation of tumors through methylation, a primary cause of MSI in endometrial tumors, and to distinguish pathways of endometrial cancer development. Several other studies in endometrial cancer have examined genes that are inactivated by promoter methylation including the APC tumor suppressor and the progesterone receptor. MSI and mutations of the gene *PTEN* I occur in complex atypical hyperplasia, the precursor to endometrial cancer. Recently, it was discovered that some normal endometrial glands lack PTEN. These PTEN deficient glands reappear through repeated menstrual cycles. These important insights into the initiation of endometrial cancer may help in the development of targeted therapies that will benefit patients with this disease.

Gene Expression Profiling. Recent gene expression profiling studies of endometrial cancers have shown a number of expression differences between the different histologic types of endometrial cancers and also with normal endometrium.

Stromal Interactions. Researchers are currently investigating whether alterations in stromal cells, extracellular matrix (ECM) as well as changes within the cell itself initiate or affect tumor development. Experiments with endometrial adenocarcinoma cells showed that introduction of stromal factors and appropriate ECM induced differentiation of more normal cells and that basement membrane proteins exert effects on the regulatory function of stromal cells.

Tumor Suppressor Genes. NCI is also supporting efforts to isolate a novel tumor suppressor gene that is involved in the development of uterine papillary serous carcinoma (UPSC), the most aggressive type of endometrial cancer. The research has identified a specific mutation in approximately 65 percent of UPSCs.

RISK FACTORS

An increased risk for endometrial cancer has been associated with estrogen-only hormone therapy, diabetes, obesity, age, lack of physical activity, HNPCC, and other medical conditions, but possible mechanisms remain obscure. Cigarette smoking and high intake of complex carbohydrates appear to reduce risk. Ongoing research in cancer etiology is looking into contributing factors, including specific medical conditions, and linkage to subsequent risk for endometrial and other cancers.

Obesity. Recent increases in endometrial cancer incidence may be linked to the increase in obesity in Americans. Risk can be increased two- to four-fold in obese women compared to women of healthy weight. NCI is sponsoring two studies on obesity and endometrial cancer-associated risk. The Four Corners Breast and Endometrial Cancer Study is investigating the effects of obesity and weight changes in Hispanic, Native American, and non-Hispanic white women. Another study is looking at the effects of phytoestrogen consumption on endometrial cancer risk in obese white, African American, and Latino women.

Hormones A woman's risk for endometrial cancer is increased by exposure to estrogen unopposed by progesterone, either endogenous or exogenous. Risk factors related to endogenous estrogenic effect include obesity, high fat diet, nulliparity, early menarche, and late menopause. NCI's Estrogen Replacement Therapy Study is a high-priority Phase 3 clinical trial designed to resolve the debate over whether women who have had early-stage endometrial cancer should take estrogen replacement.

Tamoxifen. The SERM, tamoxifen, used to treat ER-positive breast cancer and for the prevention of breast cancer in women at high risk, has been linked with an increased risk of endometrial cancer. New drugs that can be used alone or in combination therapy with tamoxifen for treatment of hormone-dependent tumors are being investigated. Alternate-substituted alkyl PCDFs are a new mechanism-based class of antiestrogens that block estrogen-induced mammary and endometrial cell/tumor growth via crosstalk between the ER and Ah receptor signaling pathways. These compounds have been shown to be relatively nontoxic, inhibit ER-positive and ER-negative mammary tumor growth, and synergize with tamoxifen to inhibit breast cancer growth and block tamoxifen-induced estrogenic activity in the uterus. Preliminary studies also indicate that selective androgen hormone receptor modulators (SahRMs) that inhibit prostate cancer cell growth may provide a new approach for treating women with breast cancer in combination with tamoxifen and SERMs.

History of Breast Cancer. Six hundred forty-eight of 37,583 women participating in the Breast Cancer Detection and Demonstration Project developed endometrial cancer during the average 13.8 years of follow-up. Women with a

personal history of breast cancer were more likely to develop endometrial cancer, yet a family history of breast cancer did not increase that risk.

HNPCC. HNPCC, responsible for 5 percent of all colon cancers, increases a woman's risk for endometrial cancer to 60 percent by age 70. Average risk is about 1.5 percent.

Other Factors. Since other medical conditions have been implicated as risks for endometrial cancer, a case-cohort study is being conducted in Denmark that will allow access to medical records for the precise diagnoses of conditions prior to development of endometrial cancer.

PREVENTION

NCI prevention studies are focusing on altering the effects of hormones necessary for prevention or therapy through route of administration; alternative, less harmful hormones or additionally regimented attenuating hormones; and new chemoprevention methods. A Phase 2 randomized study comparing medroxyprogesterone and ethinyl estradiol and norgestrel is ongoing for the prevention of endometrial cancer in HNPCC patients. Multiple studies are investigating phytoestrogens. Research includes attenuating risk associated with obesity or endometrial cancer incidence. Other NCI studies are looking at nutrition in terms of epidemiology and genetics and cancer.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

A study conducted in 101 women compared two endometrial biopsy techniques, Tao Brush and Pipelle, using both techniques during the same office visit. Sensitivity for Tao Brush was 95.5 percent, and 86 percent for Pipelle's. Both have specificities and positive predictive values of 100 percent and negative predictive values of 98 percent. Using both biopsy devices increased positive and negative predictive values to 100 percent and reduced costs.

TREATMENT

The standard treatment for endometrial cancer is surgery; hysterectomy and bilateral salpingo-oophorectomy. In women who have not completed childbearing alternative treatments that address fertility issues are being investigated, such as hormonal therapy, chemotherapy, radiotherapy, and adjuvant therapies.

Hormonal Therapies. A Phase 2 trial is comparing an estrogen blocker and receptor modulator in patients with recurrent, metastatic endometrial cancer. An NSABP study found that progesterone exerts molecular effects in cancerous endometrial cells including cyclin p21 and p27 induction, decreasing proliferation and inhibiting invasion. In progesterone receptor B expressing cells, it induces a secretory phenotype. Array analysis also showed inhibition of a number of cellular adhesion molecules. Another study showed that in poorly differentiated endometrial cancer cells, the introduction of progesterone receptors A and B allowed progestin to re-exert regulatory effects on proliferation.

Targeted Therapies. NCI treatment studies focus on comparison of different chemotherapies, alone or in combination, and with or without radiotherapy. Most trials are in Phase 1 or ½. Side effects of therapy and quality-control issues in radiation equipment are also being investigated. The more aggressive endometrial cancer, type 2, is a HER/neu-overexpressing tumor that should theoretically respond to Herceptin® treatment. Several studies, one in combination with traditional chemotherapy, are in progress. Erlotinib, an epidermal growth factor receptor inhibitor, and flavopiridol, another kinase inhibitor, are being tested in Phase 1 and 2 studies for advanced endometrial cancers.

LUNG AND OTHER TOBACCO-RELATED CANCERS

Lung cancer is the leading cause of cancer death for men and women in the United States, claiming the lives of an estimated 157,200 people in this country each year. The average annual rate of invasive lung and bronchus cancer among American women between 1995 and 1999 was 51.4 per 100,000. It is estimated that lung cancer will affect 80,100 women in 2003 and approximately 68,800 will die from lung cancer. Although incidence and mortality rates in men have been declining since the late 1980s, these rates for women continued to increase into the 1990s, leveling off since 1991 for incidence and 1995 for mortality. Since 1987, more women have died each year of lung cancer than of breast cancer, which until that year had been the major cause of cancer death in women for more than 40 years. High lung cancer mortality rates reflect our limited ability to detect lung cancer at an early and potentially more curable stage. Through the use of available detection methods, most people are diagnosed in advanced stages

of the disease, and only 15 percent survive for 5 years. Survival improves dramatically, to 49 percent, when the disease is identified and treated early.

Smoking, a preventable factor, has been implicated in many cancers of concern to women including: lung, cervical, breast, endometrial, and ovarian. NCI has taken the lead in a public/private partnership effort to address the high rate of tobacco-related cancers in women. A meeting, held in February 2003, *Women, Tobacco, and Cancer: An Agenda for the 21st Century*, assembled researchers, clinicians, and members of the advocacy community to identify gaps and research priorities, and to identify and prioritize needs in dissemination and application. Recommendations from that meeting will provide the basis for the development of action plans to increase our understanding of the sex-based differences in women's smoking behaviors, susceptibility to tobacco addiction and tobacco-related cancers, and translation of current knowledge to effective prevention and treatment interventions.

NCI's Lung Cancer PRG released a report in August 2001 that assessed the state of the science and recommended future research-related priorities for lung cancer. The PRG recommended the implementation of interdisciplinary, multi-institutional consortia; emphasized the need for continued research on the genetic, social, and biobehavioral aspects of tobacco control; and the need to better elucidate the contributions of injury, inflammation, and infection on lung cancer development. The report is available at http://prg.nci.nih.gov/lung/finalreport.html.

Transdisciplinary Tobacco Use Research Centers (TTURCs). Launched in 1999 under the joint sponsorship of NCI, the National Institute on Drug Abuse, and the Robert Wood Johnson Foundation, TTURCs are helping to provide the needed infrastructure for tobacco research across many disciplines. TTURC researchers are tackling a wide range of topics, including genetic susceptibility, animal models of behavior, sociocultural factors, innovative treatments, and research on health care policy and the bioethical implications of tobacco control. The Centers will accelerate the development of interventions to control tobacco use, speed the transfer of these approaches to communities nationwide, and train a new generation of tobacco control researchers.

Lung Cancer SPOREs. NCI currently funds seven lung cancer SPOREs. The Lung SPORE at the University of Pittsburgh Cancer Institute is studying the mechanisms for increased susceptibility to lung cancer in women.

TOBACCO-RELATED CANCERS

While lung cancer is the leading tobacco-related cancer, the following cancers in women are also associated or linked with exposure to tobacco smoke.

Endometrial Cancer. Some research suggests that female smokers have half the risk of nonsmokers for developing endometrial cancer. Though the precise mechanism is unknown, nicotine has been shown to decrease the levels of estrogen, which might decrease the growth of estrogen-sensitive tumors such as endometrial cancer and some breast cancers.

Colon Cancer. The PLCO Cancer Trial sponsored by NCI has reported an association between smoking, polyps, and colorectal cancer. Previous studies have shown that smoking increased the risk by two-fold of colon cancers that display MSI, seen in 15 percent of colon cancers. MSI increased with the amount of cigarettes smoked, the duration of smoking, and the age of smoking initiation. The time from smoking initiation to colon cancer diagnosis could be 35 years, which could explain how colon cancer rates during 1990s increased subsequent to smoking increases in the 1970s.

Cervical Cancer. Active cigarette smokers were identified as having a two-fold greater risk of developing cervical cancer. Risk appears to be dose dependent for smokers and nonsmokers exposed to environmental tobacco smoke. The findings of increased amount of tobacco-specific cancer-causing agents in the cervical lining of smokers may provide the mechanism for initiation of disease.

BIOLOGY

Molecular Characterization. The MMHCC developed a mouse model for lung adenocarcinoma, commonly found in tobacco users. The model has been instrumental in identifying a pathway for tumorigenesis. Researchers have recently reported the ability to discern patterns of gene expression for squamous cell carcinoma and adenocarcinoma, two common types of non-small cell lung cancers (NSCLC) that account for 80 percent of lung cancers.

Although nicotine is not considered a carcinogen, recently published data suggests that it plays a role in making cells resistant to apoptosis, allowing them to survive longer and undergo cancerous transformation. These findings provide evidence for treatments directed toward inhibiting survival pathway initiation and imply that nicotine replacement therapy is not without hazards, though their use to quit smoking would outweigh cost of continued tobacco use.

RISK FACTORS

Smoking. Some research has shown that smoking increases the risk for tobacco-related cancers more in women than in men. Current research is looking at the differences between how men and women metabolize tobacco carcinogens, express related genes, and repair DNA.

Lung cancer mortality is about 13 times higher among current female smokers than among women who have never smoked and former smokers who retain a heightened cancer risk for the remainder of their lives. Despite these facts, many women continue to smoke and many young girls start smoking. As smoking in adult women began to decline, rates in teenage girls rose sharply. In 2000, almost 30 percent of high school senior girls reported smoking a cigarette within the last 30 days, a decrease from 1999 when tobacco use peaked at 35 percent among teenage girls. Between the mid-1970s and the early 1990s, smoking rates in African American girls declined substantially while rates among white girls only experienced a small decline. Currently, African American girls are less likely to be smokers than white girls. The *2001 Surgeon General's Report on Women and Smoking* describes prevalence rates in U.S. females. Rates were highest among Native Americans and Alaskan Natives (34.5 percent); white women were next (23.5 percent), followed by African American women (21.9 percent). Hispanic and Asian/Pacific Islander women have rates of 13.8 percent and 11.2 percent, respectively. During pregnancy, women will stop smoking, either with assistance or spontaneously, but 12 months after delivering, 67 percent will have resumed smoking. By educational level, smoking prevalence is nearly three times higher among women with 9 to 11 years of education than among women with 16 or more years of education.

Environmental Tobacco Smoke. Each year, about 3,000 nonsmoking adults die of lung cancer as a result of breathing second-hand smoke. Recent epidemiologic studies of nonsmoking women exposed to tobacco smoke in the home estimate that there is about a 20 percent higher risk for lung cancer in these women than in unexposed women. 3 hours of second-hand smoke per day increases cervical cancer risk by three-fold. A study of nonsmoking women in China found an association between levels of exposure to home fuel in poorly ventilated homes and development of lung cancer.

Genetic Epidemiology of Lung Cancer and Smoking Study. NCI will support an interdisciplinary case-controlled study on how tobacco and genes influence both lung cancer and smoking by incorporating the study of siblings and an extensive biospecimen collection. Another study in Italy, exploring the genetic determinants of lung cancer and smoking, will also look at gene-environment interactions.

Cancer Survivors. An NCI study reported that people who received chemotherapy, radiotherapy, or both for the treatment of Hodgkin's Disease are at increased risk for developing lung cancer. Those who also smoke increase their risk about five-fold. Survivors of childhood cancer were less likely to smoke than the general population; however, those diagnosed during late childhood, those with lower income, and those with less education became smokers more often than their opposing counterparts. Survivors who began smoking were more likely to continue the habit if they began smoking after the age of 13, were less educated, or developed brain cancer that required radiation treatment. Analysis of these patterns is important for smoking prevention and cessation efforts in high-risk groups.

PREVENTION AND CONTROL

NCI, through public and private partnerships, promotes research and interventions in tobacco surveillance, prevention, and control in all populations. Some of these efforts include State and Community Tobacco Control Intervention, Youth Prevention and Cessation Research, and Monitoring Progress in Tobacco Control. Resources, such as the Tobacco Intervention Research Clinic, the Smoking Cessation Service, and the Smoking and Tobacco Control Monograph series are available to researchers and the public through the Tobacco Control Research Branch, http://dccps.nci.nih.gov/tcrb/.

Current NCI activities include:

- $ **Studies on Tobacco Use and Addiction in Women.** Studies on reducing tobacco use by pregnant women are focused on helping low-income women quit, testing the ability of women's partners to assist them in quitting, and preventing relapse after delivery. Another study examines the relationship between smoking and major depressive disorder, a problem that disproportionately affects women. NCI also is funding a major study of African American women's health that includes an examination of smoking behavior.
- $ **Smoking Cessation During Pregnancy.** A study sponsored by NCI's Tobacco Control Research Branch includes partner-assisted intervention for pregnant smokers, acceleration of progress in smoking cessation in pregnancy, and motivational enhancement therapy for pregnant smokers.
- $ **Efficacy of Exercise as an Aid for Smoking Cessation.** Researchers at the Miriam Hospital and Brown University School of Medicine studied whether sedentary female smokers in a behavioral smoking cessation program would benefit from vigorous exercise. This study demonstrates that vigorous exercise, used in conjunction with a comprehensive cognitive-behavioral smoking cessation program, leads to improved rates of smoking abstinence.
- $ **Nicotine Addiction.** An NCI study demonstrated that variations in the two genes that regulate dopamine are related to the age at which a person started smoking, the likelihood of being a current smoker, and the length of periods of smoking abstinence. Scientists continue to investigate whether a specific variation in the dopamine receptor gene will make an individual less likely to smoke, or if they smoke, if it would make them less likely to become addicted. Complementary studies conducted by TTURC investigators have found regulator genes for dopamine activity that contribute to identifying which smokers will be able to quit. These genes do not appear to affect the success of cessation treatment drug bupropion to aid in cessation. Prenatal exposure to nicotine was found to increase the probability of progressing to regular use. Other NCI-supported studies in teenagers attempting to quit smoking found nicotine withdrawal symptoms as soon as 1 month after smoking initiation.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

The National Lung Screening Trial was recently initiated to determine whether spiral computerized tomography (spiral CT) or chest X-ray will reduce lung cancer mortality prior to symptom onset. The 50,000 patient, 30-site study is being coordinated by NCI through two established networks, PLCO and American College of Radiology Imaging Network. Blood, sputum, and urine samples have been obtained for future biomarker research.

The American College of Surgeons Oncology Group, an NCI-sponsored network, is evaluating PET for lung cancer staging. Another program, Novel Imaging Technologies, facilitates new imaging technology through collaborative efforts between academia, industry, and foreign institutes. A group of NCI-supported investigators are working on the next-generation PET/CT scanner for greater localization and evaluation in difficult cancers.

Studies in the Director's Challenge program, http://dc.nci.nih.gov/, have developed methods in gene expression profiles to evaluate survival prognosis after surgery, in patients with early-stage NSCLC.

CANCER CONTROL, SURVIVORSHIP, AND OUTCOMES RESEARCH

Quality of life (QOL) issues associated with lung cancer are being investigated by NCI-supported scientists through self-reporting by 5-year survivors of NSLC. The evaluation was designed to look into pulmonary function, depression and anxiety, tobacco use, social and spiritual well-being, and demographics as they affect QOL. Depression was strongly associated with lower QOL, while co-morbid conditions were weakly indicative of QOL. It was noted that non-white participants assessed at higher QOL and mental health than whites. African Americans diagnosed with advanced NSCLCs and treated with systemic chemotherapy were found to present with poor performance and greater weight loss. Findings of the studies suggest that socioeconomic status may play an important role in QOL.

COLORECTAL CANCER

The incidence and mortality rates of colorectal cancer in both women and men have declined modestly or remained the same over the past decade. It is estimated that 74,700 women in the United States will be diagnosed with cancer of the colon or rectum in 2003 and an estimated 28,800 women will die of the disease by the end of the year, making colorectal cancer the third leading cause of cancer death among women in the United States. Native Alaskan women have the highest incidence and mortality rates due to colorectal cancer, followed by African American women, while

Native Americans of New Mexico have the lowest rates. It is estimated that deaths due to colorectal cancer could be reduced as much as 50 percent if current screening techniques were implemented as recommended.

In April 2000, NCI released the report of the Colorectal Cancer Progress Review Group. The national agenda identified an expansion of the current fundamentals through cooperation, collaboration, and new technologies as vital to advancement. The complete report, *Conquering Colorectal Cancer: A Blueprint for the Future* is available at http://prg.nci.nih.gov/colorectal/finalreport.html. NCI will be preparing and issuing a progress report on the implementation of the PRG's recommendations in 2004.

BIOLOGY

There is evidence that the addition of methyl groups to stretches of DNA where the C and G nucleotide pairing is repeated can lead to inactivation of genes involved in DNA repair and tumor initiation and progression. Additional research has discovered a connection between gene methylation and MSI, which may elucidate pathways for colorectal cancer development.

RISK FACTORS

A number of studies are currently investigating risk factors associated with colorectal cancer, including the role of IGF-1 and its binding proteins; insulin; diet; nutrient levels, such as folate, vitamin D, and antioxidants; postmenopausal hormones; smoking behaviors; BMI, physical activity, and energy fibers.

Obesity. Reports have shown that men with a high BMI are at increased risk for colon cancer. The relationship between BMI and colon cancer in women is more complex. Obesity is associated with increased risk of colon cancer in premenopausal women, but not in postmenopausal women. Risk may be modified by high levels of physical activity and is opposite to the relationship found in obesity and breast cancer where post-menopausal obesity increases risk.

Diet and Exercise. The roles of diet, energy balance, and physical activity in the etiology of colorectal cancer remain unclear. In animal studies, both saturated and polyunsaturated fatty acids from vegetable sources increased cancer risk, while diets lower in calories and high in dietary fiber, fruits, and vegetables reduce risk. The most consistent epidemiological findings for lowering risk are maintenance of a healthy body weight, exercise, and vegetable consumption. Increased colon cancer risks are seen in those with low intakes of folate, calcium, and vitamin D. Investigators in the recently completed Polyp Prevention Trial found no evidence after 4 years of follow up, that adopting a low-fat, high-fiber, fruit and vegetable-enriched eating plan reduced the recurrence of colorectal polyps, frequently a precursor of colorectal cancer. Continued follow-up of these patients may lead to further understanding of the long-term impact of diet on neoplasia. Alcohol consumption and a sedentary lifestyle have been associated in some, but not all, studies with an increased risk of colorectal cancer.

Polyp Biomarkers Study. In collaboration with the Veterans Administration (VA), NCI is establishing a biological specimen bank within an ongoing VA Cooperative Study, to examine characteristics of and risk factors for the presence of large and small polyps.

Colon Cancer Family Registries (CFRs). NCI currently supports six primary registries of familial colon cancer located throughout the world. These registries, established in 1997, assemble and maintain comprehensive lists of families with histories of colon cancer, including those resulting from familial adenomatous polyposis (FAP) syndromes and HNPCC. The registries bank blood samples and tumor biopsies for research purposes and include information on race and ethnicity, diet, and lifestyle information.

CGN, SEER, Colon CFRS. Eight hundred pairs of siblings or close relatives, where one individual has been diagnosed with colon cancer, are being recruited to identify genetic loci significant to the disease. The investigations will be conducted in individuals where there is no known HNPCC or FAP in hope of identifying cancer susceptibility regions, http://epi.grants.cancer.gov/CCFR/index.html.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Cancer-Screening Practices. New efforts are under way to increase awareness of screening benefits and treatment for colon cancer, including the CDC-led, broad-based educational campaign "Screen for Life." NCI has launched a study to understand how screening for colorectal cancer is being conducted in the United States and to help identify barriers to screening and appropriate follow-up. Investigators from NCI, CDC, and HCFA are collaborating on a study designed to obtain nationally representative data on the physician and health system factors that may affect the use of screening and diagnostic follow-up related to early detection of colorectal cancer in community practice. NCI also has a formal working relationship with the CDC on colorectal cancer-screening awareness programs. Disparity issues for colorectal cancer exist, in part, because of low screening rates among low-income and minority populations. NCI is funding numerous studies related to increasing detection and diagnosis in racial and ethnic minorities and in those historically underscreened by making health communications culturally friendly and studying community-based primary care for future intervention approaches.

Noninvasive diagnosis, detection, and screening methods for colorectal cancer are being developed and tested. A team of NCI-supported investigators have been testing for tumor-associated alterations in cancer cells shed in stool samples. Studies are under way to determine the specificity of these markers in symptomless patients.

PLCO Trial. Flexible sigmoidoscopy for colorectal cancer screening and follow-up will continue for 14 years following enrollment in PLCO. The study results will help to determine whether screening tests will reduce the number of deaths from colorectal, lung, prostate, and ovarian cancers. An etiologic component of the trial will collect biospecimens from a subset of participants to identify risk factors for colorectal adenoma and cancers.

Prognostic Indicators. Current prognostic indicator assessment relies on diagnostic pathology methods. Recent research on molecular markers has identified allelic imbalance, when chromosome pairs are different from one another, as a potential prognostic marker. Digital single nucleotide polymorphism analysis, a technology developed in SPOREs, has been able to accurately and reliably identify allelic imbalance in the two colorectal cancer relevant chromosomes, 8 and 18. This technology has shown that 42 percent of patients with allelic imbalance in both chromosomes had recurrence within 5 years while 26 percent of patients with allelic imbalance in one chromosome had recurrence within 5 years. Gene expression profiles studies in the Director's Challenge program, http://dc.nci.nih.gov/, are under way to determine profiles that discern those cancers that will recur after surgery, when metastasis will occur, and response to chemotherapy. Results so far indicate that the expression of gene clusters predict cancer cell behavior.

PREVENTION

NSAIDs. Nonsteroidal anti-inflammatory drugs block the COX-1 enzyme, required for healthy mucosal lining, and the COX-2 enzyme, which is produced in response to inflammation and precancerous tissue, such as polyps. Celecoxib (Celebrex), a selective COX-2 inhibitor, has been approved by the FDA for the treatment of osteoarthritis and adult rheumatoid arthritis. NSAID studies noted lower incidences of colorectal polyps, colorectal cancer, and death by colorectal cancer, which spurred further investigation and sponsorship of celecoxib studies by NCI. Ongoing clinical trials are investigating efficacy of celecoxib in reducing polyp occurrence, as well as its effect on cellular and molecular biomarkers in rectal mucosa. Other studies are in progress to identify biological markers for cancer progression for noncancerous polyps. NCI studies have found that in persons with surgically removed precancerous polyps, a baby aspirin (80 mg of aspirin) can reduce the risk of recurrence by 19 percent, and by 40 percent in persons with advanced adenomas. Larger doses did not show significant changes in either polyps or advanced adenomas.

Diet. NCI is supporting studies in women of Shanghai, looking at potential protective effects of low fat diet against colorectal cancer. Investigators using data from the Nurses' Health Study, the Health Professional Follow-up Study, and the Physician's Health Study have found strong evidence that consuming about 700 mg of calcium per day can reduce the risk of developing colon cancer in both men and women. Other results have shown that multivitamins with folate, diets rich in both folate and methionine, and alcohol consumption lower than moderate to heavy, may decrease colon cancer risk in women with family histories of the disease.

TREATMENT

FOLFOX4. Oxaliplatin is an investigational drug, used in conjunction with two routine cancer drugs in an experimental regimen, FOLFOX4. In a large, randomized clinical trial, patients on FOLFOX4 showed significant improvement outcomes, including longer life span, longer time to tumor progression, better response rate and fewer severe side effects.

Gleevec. Originally approved in May 2001 for the treatment of chronic myelogenous leukemia, NCI has launched clinical trials for the safety and efficacy of this monoclonal antibody for the treatment of gastrointestinal stromal tumors (GIST) since researchers found evidence of its success in treating this rare form of cancer. Results showed dramatic reduction of tumor size in 53 percent of patients and decreased growth rates in another 28 percent of patients. Despite development of drug resistance, 88 percent of patients were living 1 year after treatment initiation.

QUALITY OF LIFE

Laparoscopic surgery for colon cancer resulted in slightly shorter hospital stays and less postoperative pain medication while in the hospital compared to standard surgery patients. However, quality of life measures and symptom management within the first 2 months after surgery are similar for both procedures. These studies were conducted in 428 men and women with colon cancer already enrolled in the Clinical Outcomes of Surgical Therapy trial, which is being conducted in 37 centers in the United States and Canada.

AIDS-ASSOCIATED MALIGNANCIES

PREVALENCE

AIDS and HIV infection continue to be major public health concerns. From 1981 to 2001, 816,149 cases of AIDS were reported to the CDC, 18 percent of which were in women. Heterosexual transmission of HIV increased from 3 percent in 1985 to 28 percent in 2001. 65 percent of HIV-positive women are infected by this route. Approximately 506,154 persons are currently living with HIV infection or AIDS in the United States. Of those, 141,048 adults and adolescent women are living with AIDS, and 49,226 are living with HIV infection. In 2001, 41,744 new cases of AIDS were reported to the CDC; one third were in women. There were also 35,051 new cases of HIV infection reported; however, this is likely an underestimate since not all states report new cases.
While the numbers of deaths per year in the United States due to AIDS has decreased in the era of highly active antiretroviral therapy (HAART), the numbers of persons living with the disease has increased. The longer life expectancy of HIV+ people with access to HAART may increase their cumulative risk of developing cancer to rates similar to solid organ transplant recipients whose lifetime risk of cancer is increased due to iatrogenic immune suppression.

AIDS-Associated Malignancies The long-term risks of developing cancer for HIV+/AIDS patients are not yet known. Malignancies occur in more than 30 to 40 percent of HIV+ patients during the course of their disease and include: non-Hodgkin's lymphoma, cervical cancer, anal cancer, and Kaposi's sarcoma (KS). Although KS is extremely rare among women, non-Hodgkin's lymphoma (NHL) currently ranks sixth in overall female cancer incidence and mortality. In addition, there is an increased incidence of NHL in women from the pre-HAART to HAART period. The risk of cervical neoplasia is five times higher in women with HIV infection than in uninfected women, due to the extraordinarily high prevalence of oncogenic HPV infection among HIV-seropositive women. Cervical HPV rates in HIV-infected women are 43 percent versus 24 percent in uninfected women. Rates for anal HPV in HIV-infected women are 79 percent, compared to uninfected women, whose rates are 53 percent.

Women's Interagency HIV Study (WIHS) Since 1995, NCI has provided supplemental funds to support malignancy studies in the NIAID/NICHD/NIDA/NIDCR-funded WIHS, the largest U.S. study of HIV infection in women. HIV-infected women have increased incidence rates for Kaposi sarcoma (>200-fold), non-Hodgkin's lymphoma (23-fold), and lung cancer (10-fold) when compared to SEER rates. No significant increases have been detected among HIV-infected and high-risk uninfected WIHS women for lung cancer after adjusting for cigarette smoking. Only one confirmed case of invasive cervical cancer has occurred to date in an HIV-infected woman. Despite concerns to the contrary, no increased risk of breast cancer or unusual types of breast tumors have been detected in over 5,000 woman-years of follow-up. HIV-infected women who initiated highly active antiretroviral therapy against HIV experienced significant reductions in overall cancer risks. WIHS women have high rates of infection with oncogenic tumor viruses, including hepatitis C and human herpes virus 8.

TREATMENT

Aids Malignancy Program (AMP) NCI developed a multi-component AMP, http://ctep.cancer.gov/resources/aids.html, to assist the research community in studying the interplay of viruses, immune dysfunction, aberrant growth factor expression, and the development of cancer in AIDS patients, with the goal of developing more effective treatment regimens. The main components of the program are the AIDS-Associated Malignancies Clinical (AMC) Trials Consortium (http://www.amc.uab.edu) and the AIDS and Cancer Specimen Resource (ACSR) (http://acsr.ucsf.edu). The ACSR contains or provides access to over 100,000 specimens collected from cohort studies, clinical trials, and other research.

The AMC unites 15 main member sites that conduct innovative treatment trials for AIDS-associated malignancies, providing access to tissue specimens and clinical data from patients. Important clinical information from completed AMC trials includes: Oral 9-cis-retinoic acid was shown to be an active anti-tumor drug for AIDS-related KS with an overall response rate of 37 percent; CHOP or a modified dosage of CHOP chemotherapy is an effective and tolerable treatment for NHL in HIV+ patients on HAART; IFN-α2β administered to HIV+ KS patients on protease inhibitors was well tolerated with overall response of 39 percent; in a phase I trial, Oral COL-3 administered once daily to HIV+KS patients is well tolerated, with overall response of 44 percent; and a phase III study indicated that IM862 is ineffective against AIDS-KS, in contrast to earlier phase I and II trials.

EPOCH An NCI study of dose-adjusted EPOCH (etopside, prednisone, vincristine, cyclophosphamide, doxorubicin) chemotherapy with HAART suspension for untreated AIDS-Related Non-Hodgkin's lymphoma (ARL) patients showed disease-free and overall survival of 92 and 60 percent, respectively, at 53 months median followup. Results seemed to correlate with high MIB-1 and possible upward CD4 risk migrations and providing emphasis for the importance of tumor biology in treatment outcomes. The results also suggest that by forestalling immune depletion, HAART has shifted tumor pathogenesis and confers no specific benefit during chemotherapy treatment.

A European-U.S.study showed a reduction in HIV transmission in pregnant women treated with antiretroviral therapy, caesarian section, with greater birth weight babies, and higher CD4 cell count.

Requests for Applications (RFAs) and Program Announcements (PAs)
Relevant to Women's Health, FY 2001-2002

N02-CP-21005-50
Defining and Validating Biomarkers of Risk for Cervical Cancer
The purpose of this RFP is to collect and store cervical tissue specimens that will be used for DNA and RNA analyses in women representative of the four natural history categories in cervical neoplasia: normal, HPV-positive, precancer, and cancer. The main focus of the research is to identify and validate biomarkers at different stages of cervical neoplasia that may be predictive of disease.

PA-01-091
Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses (FLAIR)
This PA provides a flexible system within the Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) programs to accommodate special needs of the complex drug discovery and development process, from basic discovery through proof-of-principle demonstration in clinical trials, allowing for projects to be presented at all stages of the drug discovery and development process.

PA-02-001
Exploratory Grants for Behavioral Research in Cancer Control
The objective of this PA is to conduct creative, novel research in the behavioral aspects of the cancer control continuum from prevention to end-of-life care and to increase scientific knowledge about health behaviors and health care practitioners' behaviors.

PA-02-002
Clinical Cancer Therapy Research
The overall aims of this initiative are twofold: (1) to stimulate development of innovative therapeutic clinical trials with or without laboratory correlations and (2) to support innovative correlative laboratory studies linked to therapeutic clinical trials to foster the development of interactions between basic science laboratories and clinicians performing the clinical trials.

PA-02-005 (NCI, AHRQ)
Economic Studies in Cancer Prevention, Screening, and Care
Through this PA, the National Cancer Institute (NCI) and the Agency for Health Care Research and Quality (AHRQ) will support research to generate new economic knowledge that will promote the optimal design of cancer prevention and control trial studies and interventions, to facilitate the formulation of effective health care policy related to cancer prevention and control, and to increase the overall understanding of economic aspects of cancer prevention, screening, and care.

PA-02-043 (NIH)
Social and Cultural Dimensions of Health
NCI joins other NIH offices and institutes to support research to (1) elucidate basic social and cultural constructs and processes used in health research, (2) clarify social and cultural factors in the etiology and consequences of health and illness, (3) link basic research to practice for improving prevention, treatment, health services, and dissemination, and (4) explore ethical issues in social and cultural research.

PA-02-169 (NIA, NCI)
Integrating Aging and Cancer Research
The National Institute on Aging (NIA) and NCI will support studies directed at understanding aging and age-related aspects of cancer in older persons, with research spanning the scientific spectrum of cancer control for early detection, diagnosis, prevention, treatment, prognosis, and survivorship.

PA-03-003
Exploratory Studies in Cancer Detection, Diagnosis, and Prognosis
The major goals of this PA are to promote the initial evaluation of new molecular or cellular characteristics of premalignant cells or tumors to identify new biomarkers; the development of assays that will be useful for cancer

detection, diagnosis, and/or prognosis; and the evaluation of assays through translational studies to decide whether potential clinical utility justifies further investment.

PA-03-021
Molecular Targets for Cancer Drug Discovery (SBIR/STTR)
The objective is to support young, start-up biotechnology companies and more established firms to conduct preclinical studies toward developing novel drugs for cancer treatment and prevention, with a focus on new molecular targets and agents that modulate them.

PA-03-024 (NCI, NIAAA, NIDA, NICHD)
Molecular Epidemiology of Cancers Associated with Acquired Immunodeficiency
The purpose of this project is to better understand the molecular epidemiology and role of cofactors in the etiology and pathogenesis of preneoplastic conditions and cancers occurring among persons infected with human immunodeficiency virus (HIV), specifically cancers associated with viruses such as human papillomavirus, Epstein Barr virus, human herpes virus 8/Kaposi sarcoma-associated herpes virus, and hepatitis B and C.

PAR-01-101; PAR-01-102 (NCI; NCI, NIEHS)
Development of Novel Technologies for In Vivo Imaging (Phased Innovation Award and SBIR/STTR)
These initiatives are primarily intended to facilitate the development of novel imaging technologies for early detection, screening, diagnosis, or image-guided treatment of cancer and to facilitate clinical evaluation studies of the development that are specifically limited to proof of concept.

PAR-02-037
Small Grants Program for Behavioral Research in Cancer Control
This program is designed to conduct behavioral research investigations in cancer prevention and control. The following program areas focused on behavior and cancer may be supported: screening and early detection, health promotion research, tobacco control research, applications research, health communications and informatics research, basic biobehavioral research, applied surveillance, survivorship, and health disparities.

PAR-02-042 (NCI, AHRQ)
Colorectal Cancer Screening in Primary Care Practice
NCI and AHRQ will promote research to develop the capability for gathering patient, provider, practice, and clinical data and/or conducting interventions to assess and enhance colorectal cancer screening delivery, utilization, and outcomes.

PAR-02-126
Specialized Programs of Research Excellence (SPOREs) in Human Cancer for the Year 2003
NCI supports SPOREs in organ-specific cancers. Applicant institutions must be able to conduct the highest- quality, balanced, translational research on the prevention, etiology, screening, diagnosis, and treatment of a specific organ-site cancer. Current SPOREs are funded in Brain, Breast, Gastrointestinal, Genitourinary, Gynecologic, Head and Neck, Lung, Lymphoma, Ovarian, Prostate, and Skin Cancers.

PAR-03-005
Quick Trials for Novel Cancer Therapies
The focus of this PA is on rapidly ushering translational research through pilot, Phase 1, and Phase 2 clinical trials to ensure timely exploitation of cancer therapeutic approaches, including the development of new cancer prevention agents.

RFA-AT-01-002 (NCCAM, NCI, NIAID, NIMH, NINR)
Complementary and Alternative Medicine (CAM) at the End of Life for Cancer and/or HIV/AIDS
NCI joins the National Center for Complementary and Alternative Medicine in inviting applications to generate scientific knowledge on CAM therapies that alone or in combination with conventional treatment modalities have the potential to improve the quality of life for persons with cancer or HIV/AIDS who are at the end of life.

RFA-CA-01-013
Cancer Care Outcomes Research and Surveillance Consortium (CanCORS)
This RFA, focused on lung and colorectal cancer, will support the development of a system for obtaining details about cancer care beyond the initial diagnosis and limited treatment data that are now routinely collected in high-quality population-based cancer registries. This research will help build the information base needed for measuring and improving the quality of cancer care in the United States, including an examination of disparities in cancer care and outcomes and identifying ways to lessen those disparities.

RFA-CA-02-001
Tissue and Biological Fluids Banks of HIV-Related Malignancies
NCI invites applications from consortia of institutions for cooperative agreements to bank tissue and biological fluids and to maintain associated clinical data from patients with HIV-associated malignancies to be utilized for research, by the research community at large, on the pathogenesis of HIV-associated malignancies and development of more effective therapies.

RFA-CA-03-005
Chemoprevention of Estrogen Receptor (ER)-Negative Breast Cancer Preclinical Studies
The purpose of this initiative is to support the preclinical development and evaluation of chemopreventive strategies that could be rapidly translated to clinical studies and are applicable to women at high risk for development of ER-negative breast cancer.

RFA-CA-03-010
Comprehensive Minority Institution/Cancer Center Partnership
The purpose of this project is to increase the cancer research capabilities at the minority-serving institutions; to increase the number of minority scientists engaged in cancer research and other related cancer activities; and to improve the effectiveness of NCI-designated cancer centers in developing and sustaining activities focused on the disproportionate incidence, mortality, and morbidity in minority populations in the region the cancer center serves.

RFA-CA-03-012
Minority-Based Community Clinical Oncology Program
The Community Oncology and Prevention Trials Research Group (COPTRG), Division of Cancer Prevention, will support domestic institutions with the capability and intent to serve new cancer patients largely from minority populations through cooperative agreements to support cancer clinical trials, to expand the cancer prevention and control research effort using the minority-based Community Clinical Oncology Program (CCOP) network, and to evaluate minority-based CCOP performance and its impact in the community.

RFA-CA-03-015
In Vivo Cellular and Molecular Imaging Centers (ICMICs)
This initiative is designed to capitalize on the extraordinary opportunity for studying cancer noninvasively and, in many cases, quantitatively due to recent advances in molecular imaging modalities, as well as molecular and cellular biology, with an emphasis on multidisciplinary approaches to discover and develop new projects.

RFA-CA-03-016; RFA-CA-03-016 (NIH, ODS)
Diet, DNA Methylation and Other Epigenetic Events, and Cancer Prevention
Diet, DNA Methylation and Other Epigenetic Events, and Cancer Prevention: Competing Supplements
NCI and the Office of Dietary Supplements (ODS), NIH, will support new and existing projects to encourage collaborative research leading to the elucidation of mechanism(s) by which dietary factors influence epigenetic processes, as well as increasing the understanding of these processes in cancer prevention and tumor incidence and behavior.
RFA-CA-03-018

Cooperative Planning Grant for Cancer Disparities Research Partnership Program
Grants funded by this RFA will support the planning, development, and conduct of radiation oncology clinical research trials in institutions that care for a disproportionate number of medically underserved, low-income, ethnic, and minority populations but have not been traditionally involved in NCI-sponsored research. These grants will similarly support nurturing partnerships between applicant institutions and committed and experienced institutions actively involved in NCI-sponsored cancer research.

RFA-OH-01-001 (NIOSH, NCER, NIEHS, NCI)
Endocrine Disruptors: Epidemiologic Approaches
This interagency program by NIOSH, Environmental Protection Agency, NIEHS, and NCI will support research on the relationship between exposure to endocrine disruptors and adverse health effects in humans, particularly reproductive and developmental, with a focus on epidemiologic approaches.

SELECTED MEETINGS OF INTEREST

(Sponsored or co-sponsored by NCI)

The National Conference on Tobacco and Health Disparities
(Palm Harbor, FL, December 11, 2002 – December 13, 2002)

2002 National Conference on Tobacco or Health
(San Francisco, CA, November 19, 2002 – November 21, 2002)

Symposium for Nurses: How Clinical Trials at NCI Can Increase Options for Your Patients
(Bethesda, MD, November 15, 2002)

Workshop on Vaccine Development in Breast Cancer
(Bethesda, MD, September 30, 2002)

Post-Translational Protein Modification: Novel Technologies and Implications for Cancer Prevention
(Bethesda, MD, August 28, 2002 – August 29, 2002)

Applications of Bioinformatics in Cancer Detection (ABCD) Workshop
(Bethesda, MD, August 6, 2002 – August 7, 2002)

Fifth Annual Breast Cancer Faculty Intramural Retreat
(Baltimore, MD, July 17, 2002 – July 18, 2002)

NIH State-of-the-Science Conference on Symptom Management in Cancer: Pain, Depression, and Fatigue
(Bethesda, MD, July 15, 2002 – July 17, 2002)

Cancer Health Disparities Summit 2002
(Washington, DC, July 15, 2002 – July 17, 2002)

Cancer Survivorship: Resilience Across the Lifespan
(Washington, DC, June 02, 2002 – June 02, 2002)

6th International Conference on Malignancies in AIDS and Other Immunodeficiencies: Basic, Epidemiologic and Clinical Research
(Bethesda, MD, April 22, 2002 – April 24, 2002)

2nd International Conference on Cervical Cancer
(Houston, TX, April 11, 2002 – April 14, 2002)

United States - Japan Cooperative Cancer Research Program Symposium on Tobacco-Related Cancers
(Bethesda, MD, February 25, 2002 – February 26, 2002)

Epigenetics in Cancer Prevention: Early Detection and Risk Assessment Workshop
(Bethesda, MD, December 03, 2001 – December 04, 2001)

2001 National Conference on Tobacco or Health
(New Orleans, LA, November 27, 2001 – November 29, 2001)

Comprehensive Cancer Care: Integrating Complementary & Alternative Therapies
(Arlington, VA, October 19, 2001 – October 21, 2001)

Breast Cancer Think Tank (BCTT) 2001 Retreat
(Chantilly, VA, July 19, 2001 – July 20, 2001)

Bethesda 2001 Workshop - Bethesda System for Reporting Results of Cervicovaginal Cytologic Diagnoses
(Bethesda, MD, April 30, 2001 – May 02, 2001)

Fifth International AIDS Malignancy Conference
(Bethesda, MD, April 23, 2001 – April 25, 2001)

Workshop on Colorectal Cancer (CRC) Screening for Persons of Average Risk
(Bethesda, MD, March 01, 2001 - March 02, 2001)

Second 5 A Day International Symposium for Better Health
(Washington, DC, January 07, 2001 – January 09, 2001)

Nanotechnology in Early Detection of Cancer Workshop
(Gaithersburg, MD, August 30, 2001)

Trans-HHS Workshop: Diet, DNA Methylation Processes, and Health
(Bethesda, MD, August 06, 2001 – August 06, 2001)

KEY WORDS

Breast Cancer
molecular profiling, MMHCC, estrogen receptor, tamoxifen, raloxifene, cyclin E, BRCA1, BRCA2, CGAP, CGN, diet, obesity, physical activity, body mass index, The Health, Eating, Activity, and Lifestyle study (HEAL), diethylstilbestrol (DES), hormones, estrogen, progestin, prolactin, postmenopausal hormone use, oral contraceptives (OC), environmental factors, Long Island Breast Cancer Study Project (LIBSCP), DDT, DDE, PCBs, radiation, chemoprevention, Study of Tamoxifen and Raloxifene (STAR), SERMs, prophylactic surgery, MRI, PET, SPECT, digital mammography, sentinel node biopsy, proteomics, adjuvant therapy, fulvestrant, aromatase inhibitors, Anastrozole, Herceptin, high-dose chemotherapy with stem cell transplant, lumpectomy, mastectomy, health disparities, cancer survivors.

Cervical Cancer
human papillomavirus (HPV), cofactors, HLA alleles, tobacco, HIV, DES, HPV vaccine, diet, pap test, 2001 Bethesda System, HPV testing, ASCUS/LSIL Triage Study (ALTS), high-grade squamous intraepithelial lesion (HSIL), low-grade squamous intraepithelial lesion (LSIL).

Ovarian Cancer
exogenous hormones, inherited risk factors, BRCA1, BRCA2, diet, genetic polymorphism, oral contraceptives, OC, fertility drugs, prophylactic oophorectomy, proteomics, microarray technology, prognostic indicators, Early Detection Research Network, Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) Trial, 3D power Doppler ultrasound, "ovarian pap test", CGAP.

Endometrial Cancer

microsatellite instability (MSI), HNPCC, MSH2, MLH1, APC, PTEN I, CAH, gene expression profiling, stromal interactions, tumor suppressor genes, obesity, exogenous hormones, tamoxifen, SERMs, smoking, hormonal therapies, chemotherapy, radiotherapy.

Lung and Other Tobacco Related Cancers
Transdisciplinary Tobacco Use Research Centers (TTURCs), endometrial cancer, colon cancer, cervical cancer, molecular characterization, smoking, environmental tobacco smoke, cancer survivors, nicotine addiction, smoking cessation, pregnancy, National Lung Screening Trial, spiral computerized tomography (CT), PLCO, PET, quality of life.

Colorectal Cancer
methylation, MSI, obesity, diet, exercise, polyp biomarker, screening, PLCO, flexible sigmoidoscopy, prognostic indicator, NSAIDs, COX-2 enzyme, baby aspirin, celecoxib (Celebrex), diet, FOLFOX4, Gleevec, laparoscopic surgery.

AIDS-Associated Malignancies
AIDS, HIV, highly active antiretroviral therapy, non-Hodgkin's lymphoma, cervical cancer, anal cancer, Kaposi's sarcoma, AIDS Malignancy Program, Women's Interagency HIV Study.