NATIONAL CANCER INSTITUTE

Women's Health Report, Fiscal Years 2005-2006

February 2007

Office of Women's Health
Office of Science Planning and Assessment
National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

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EXECUTIVE SUMMARY

This report describes many of the activities and accomplishments of NCI's research programs in Fiscal Years 2005 and 2006 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) and AIDS-associated malignancies.

Cancer continues to take a devastating toll on American women. In 2007, an estimated 678,060 women will be diagnosed with cancer, and approximately 270,100 women will die of the disease. Despite these grim statistics, our nation is making important progress in the fight against cancer overall and in women. Cancer incidence rates for all sites, sexes, and populations combined have been stable from 1992 through 2003 after increasing since 1975; the pattern was similar for men. Incidence rates for cancer overall for women were stable from 1975 through 1979, and then increased throughout the period of 1979 through 2003. On the contrary, breast cancer incidence rates for women had a non-significant decrease from 2001 through 2003. Overall there was a 6 percent relative decline in breast cancer incidence between 2002 and 2003, including a 14 percent decrease in women aged 50-69 diagnosed with estrogen receptor positive breast cancer. The decrease in this group may be due to the recent decline in use of hormone replacement therapy (HRT) by postmenopausal women. The overall cancer death rates for all sites, sexes, and race/ethnic populations decreased from 1994 through 2003, with the annual rate of decline in men twice as large as the annual decline for women. Mortality has decreased for all cancers combined in the general population and for 10 of the top 15 cancers in women. Lung cancer death rates among women continue to increase although at a slower annual rate in more recent years. Survival rates for cancer patients diagnosed in the years 1975 to 1979 compared to those diagnosed from 1996 to 2002 show improvement overall, although the amount of improvement is slightly less for women than for men.

The National Cancer Institute (NCI) is committed to continuing efforts to reduce the toll of cancer through scientific discovery and its application to people. NCI's Office of Women's Health, organizationally located within the Office of Science Planning and Assessment, assists in planning, evaluating, and coordinating activities related to cancers in women. In addition to the extensive research supported both at the NCI and externally, through research grants, a number of specific programs and activities focus on women's cancers. The NCI Office of Women's Health provides information on these and other NCI programs on its Web site, NCI Research on Cancers in Women, http://women.cancer.gov. Additional information for the public, the cancer community, and journalists can be found on the NCI Web Site's cancer topics page, Women's Cancers, http://www.cancer.gov/cancertopics/types/womenscancers.

NCI supports broad-based research programs that apply to all types of cancer in women, men, and children. Through its strategic planning process, the Institute identifies many of the questions that need to be answered, areas of research and care that need to be supported, and infrastructure that needs to be strengthened, to ultimately reduce the burden of cancer (see http://planning.cancer.gov/planning/index.shtml). NCI supports research programs to expedite progress towards the strategic objectives described in the NCI Strategic Plan.

TO PREEMPT CANCER AT EVERY OPPORTUNITY

Understanding the Causes and Mechanisms of Cancer. The NCI research portfolio supports basic, clinical, and population research to better understand how multiple, complex factors relate to the development and progression

of cancers. This knowledge is essential to developing prevention and treatment interventions. Researchers are working to develop and apply animal models of human cancers; identify biomarkers of risk, progression, and prognosis; elucidate molecular interactions among cancer cells and their microenvironment; and develop specimen resources to provide the biologic material and supporting clinical data for research. For example: Using the proceeds of special-issue U.S. Postal stamps, the NCI has established a comprehensive program on breast cancer premalignancy encompassing prevention, etiology, biology, diagnosis and molecular epidemiology research to advance our understanding of the early events associated with premalignancy and breast cancer.

Accelerating Progress in Cancer Prevention. The NCI portfolio supports research to identify medical and behavioral approaches to cancer prevention that can be applied in public health settings. Recent advances in cancer prevention include approval by the Food and Drug Administration in June 2006 of the use of a new vaccine, Gardasil™ (Merck and Co., Inc.), which protects against the two types of HPV that cause the majority of cervical cancers worldwide. The vaccine is based on laboratory research and technology developed at NCI and has the potential to significantly improve women's health globally. NCI continues to conduct research on HPV and cervical cancer. Additionally, initial results of the Study of Tamoxifen and Raloxifene Trial, comparing two selective estrogen inhibitors, showed that raloxifene is as effective as tamoxifen in reducing breast cancer risk in participants and causes fewer side effects. The NCI partners with other federal and non-federal organizations to disseminate tobacco cessation interventions, including the national toll-free quitline, 800-QUIT NOW, the Helping Young Smokers Quit initiative, and the International Tobacco and Health Research and Capacity Building Program.

Improving Early Detection and Diagnosis. Ongoing research supports the development and dissemination of interventions to detect and diagnose early-stage malignancy with the goal of improving the odds for successful treatment and reduction in mortality. For example, the National Ovarian Cancer Early Detection Program: Screening and Genetic Study is a multi-site clinical trial that seeks to identify screening and genetic testing methods for ovarian cancer risk; identify and develop highly sensitive and specific early detection tumor markers; develop therapies based on molecular, genetic, and biochemical insights; and determine the utility of minimally invasive office procedures. Researchers working to improve screening for early detection of breast cancer in the Digital Mammography Imaging Screening Trial showed that women with dense breasts would benefit from having digital rather than film mammography.

Developing Effective and Efficient Treatments. NCI treatment research focuses on discovering, developing, and evaluating more efficient and effective treatment strategies with little or no harm to healthy tissue. In January 2006, NCI issued a rare clinical announcement to raise awareness about intraperitoneal (IP) chemotherapy for ovarian cancer. Women with ovarian cancer who received the therapy following surgery lived on average 16 months longer than women who had standard treatment, with similar quality of life. Previously, IP chemotherapy was only given to about 1 percent of women with ovarian cancer. The NCI Gynecologic Oncology Group (GOG) reported that adjuvant chemotherapy with cisplatin and doxorubicin improves survival of women advanced endometrial cancer. Additionally, GOG is conducting a phase III trial of the better tolerated carboplatin and paclitaxel therapy.

TO ENSURE THE BEST OUTCOMES FOR ALL

Understanding the Factors That Influence Cancer Outcomes. NCI is intensifying its efforts to define, foster, and support studies to improve our understanding of the diverse factors that affect the outcomes of cancer and the impact of cancer care. For example: The Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) is the largest-ever observational study of cancer care delivered in diverse, population-based health care settings. The prospective cohort study is enrolling patients with newly diagnosed lung or colorectal cancer and is collecting information on the effects of clinical practices and other influences on delivery of services and patient outcomes. The study includes patient, caregiver, and provider perspectives for diverse groups of patients over time and provides a unique opportunity to examine community practices related to palliative and end-of-life-care.

Improving the Quality of Cancer Care. NCI research supports the development and dissemination of evidence-based quality improvement interventions to ensure the delivery of high quality cancer care and improve health-related outcomes across the cancer continuum. For example: The NCI Center to Reduce Cancer Health Disparities (CRCHD) has launched an innovative Patient Navigator Research Program, focusing on four cancers for which screening tests are available: breast, cervical, prostate and colorectal. Patient navigators are trained, culturally sensitive health care workers who provide support and guidance throughout the cancer care continuum. Eight participating research institutions will provide navigators to help patients and their families manage cancer diagnoses and overcome common barriers to obtaining timely and appropriate cancer care and treatment.

Improving the Quality of Life for Cancer Patients, Survivors, and Their Families. NCI supports research on the development and dissemination of interventions to reduce the adverse effects of cancer diagnosis and treatment and improve health-related outcomes for cancer patients, survivors, their families and caregivers. For example: The Long Term Cancer Survivors Research Initiative supports research on understudied areas related to the physical, psychosocial, behavioral, and economic affects of cancers and its treatment. NCI also supports research that addresses the social, emotional and interpersonal impact of cancer and its treatment on sexual functioning and fertility in cancer survivors.

Overcoming Cancer Health Disparities. Overcoming cancer health disparities is one of the best opportunities we have for lessening the burden of cancer. NCI supports research to identify the causes, develop approaches, and disseminate interventions to overcome disparities across the cancer control continuum. For example: The Community Networks Program (CNP) aims to reduce cancer health disparities through community-based participatory education, training, and research among racial/ethnic minorities and underserved populations. The recently launched NCI Community Cancer Centers Program is a pilot to bring the latest scientific advances and high level innovative, integrated, multi-specialty care and clinical trials to populations in community-based settings.

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INTRODUCTION

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Cancer continues to take a devastating toll on American women. In 2007, an estimated 678,060 women will be diagnosed with cancer, and approximately 270,100 women will die of the disease. Despite these grim statistics, our nation is making important progress in the fight against cancer overall and in women. Cancer incidence rates for all sites, sexes, and populations combined have been stable from 1992 through 2003 after increasing since 1975; the pattern was similar for men. Incidence rates for cancer overall for women were stable from 1975 through 1979, and then increased throughout the period of 1979 through 2003. On the contrary, breast cancer incidence rates for women had a non-significant decrease from 2001 through 2003. Overall there was a 6 percent relative decline in breast cancer incidence between 2002 and 2003, including a 14 percent decrease in women aged 50-69 diagnosed with estrogen receptor positive breast cancer. The decrease in this group may be due to the recent decline in use of hormone replacement therapy (HRT) by postmenopausal women. The overall cancer death rates for all sites, sexes, and race/ethnic populations decreased from 1994 through 2003, with the annual rate of decline in men twice as large as the annual decline for women. Mortality has decreased for all cancers combined in the general population and for 10 of the top 15 cancers in women. Lung cancer death rates among women continue to increase, although at a slower annual rate in more recent years. Survival rates for cancer patients diagnosed in the years 1975 to 1979 compared to those diagnosed from 1996 to 2002 show improvement overall, although the amount of improvement is slightly less for women than for men.

NCI is committed to continuing efforts to reduce the burden of cancer through scientific discovery and its application to people. NCI's Office of Women's Health, organizationally located within the Office of Science Planning and Assessment, assists in planning, evaluating, and coordinating activities related to cancers in women. In addition to the extensive research supported at the NCI and through research grants, a number of programs focus specifically on women's cancers, including the Breast and Gynecologic Cancer Research Group in the Division of Cancer Prevention, the Breast Cancer Surveillance Consortium (BCSC) and the International Breast Screening Network in the Division of Cancer Control and Population Sciences, the Gynecologic Oncology Group (GOG) clinical trials cooperative group in the Division of Cancer Treatment and Diagnosis, the intramural Breast and Gynecologic Malignancies Faculty, and the trans-NCI HPV (human papillomavirus) Working Group.

In addition to research with a primary focus on women's health, NCI supports broad-based research programs that apply to all types of cancer in women, men, and children. 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 supported, and infrastructure that needs to be strengthened to reduce the burden of cancer in all populations. The NCI Strategic Plan, (http://strategicplan.nci.nih.gov/) released in 2006, details eight strategic objectives in two broad areas, *To Preempt Cancer at Every Opportunity* and *To Ensure the Best Outcomes for All.* NCI supports research programs to expedite progress toward these objectives:

TO PREEMPT CANCER AT EVERY OPPORTUNITY

1. *Understanding the Causes and Mechanisms of Cancer.* Research to discover the causes and mechanisms of cancer is essential to enable us to develop and apply treatments or interventions to keep cancers from starting or progressing. The NCI research portfolio supports basic, clinical, and population research to better understand how genetic, epigenetic, environmental, behavioral, and sociocultural factors relate to cancer.
2. *Accelerating Progress in Cancer Prevention.* The NCI portfolio supports research to identify medical and behavioral approaches to cancer prevention that can be applied in public health settings. Prevention research focuses on risk assessment, systems biology, behavior modifications, environmental and policy influences, medical and nutritional approaches, and training and education for research and health professionals.
3. *Improving Early Detection and Diagnosis.* Ongoing research supports the development and dissemination of interventions to detect and diagnose early-stage malignancy with the goal of improving the odds for successful treatment and reduction in mortality.
4. *Developing Effective and Efficient Treatments.* NCI treatment research focuses on discovering, developing, and evaluating more efficient and effective treatment strategies with little or no harm to healthy tissue.

TO ENSURE THE BEST OUTCOMES FOR ALL

5. *Understanding the Factors that Influence Cancer Outcomes*. NCI is intensifying its efforts to define, foster, and support studies to improve our understanding of the factors that affect the outcomes of cancer and the impact of cancer care. Research focuses on increasing our understanding of and ability to measure the environmental, behavioral, sociocultural, and economic influences that affect the quality of cancer care, survivorship, and health disparities.
6. *Improving The Quality of Cancer Care.* High quality cancer care requires delivering the full range of evidence-based interventions that are safe, patient-centered, effective, timely, efficient, and equitable. Such care must be provided with technical competence and cultural sensitivity and must foster patient choice based on informed decision making. NCI research supports the development and dissemination of quality improvement interventions and methods to measure their success in improving health-related outcomes across the cancer continuum.
7. *Improving The Quality of Life for Cancer Patients, Survivors, and Their Families.* NCI supports research on the development and dissemination of interventions to reduce the adverse effects of cancer diagnosis and treatment and improve health-related outcomes for cancer patients, survivors, and their families/caregivers.
8. *Overcoming Cancer Health Disparities*. Overcoming cancer health disparities is one of the best opportunities we have for lessening the burden of cancer. NCI's investments are speeding the development and use of interventions to combat disparities across the cancer control continuum and among all underserved populations. NCI supports research to identify factors contributing to disparities, develop culturally appropriate approaches, and disseminate interventions to overcome those disparities across the cancer control continuum from disease prevention to end-of-life care.

The participation of NCI staff in multiple, diverse scientific partnerships and collaborative activities with other federal and non-federal scientists benefits women, as well as men and children. By working with partners from public, private, and academic settings and focusing investment in strategic areas with high potential, staff take advantage of opportunities to accelerate the pace of discovery and facilitate the translation of research knowledge to clinical application. For example:

- Bringing the Benefits of Research to Patients in Their Home Communities. The NCI is launching the NCI Community Cancer Centers Program (NCCCP) in early 2007, as a pilot program to bring the latest scientific advances and the highest level of innovative and integrated, multi-specialty care to a much larger population of patients. The NCCCP complements other NCI initiatives to draw more patients into clinical trials in community-based settings; reduce healthcare disparities; prepare sites for standardizing the collection and storage of biological specimens for cancer research; link sites to national databases supporting basic, clinical, and population-based cancer research; and implement electronic medical records. Pilot sites will also share best practices and refine the overall concept as a prelude to launching a national network of research-driven cancer care at the community level.
- Energy Balance as a Way to Control Cancer Incidence. Centers for Transdisciplinary Research on Energetics and Cancer (TREC) have been developed to foster collaboration among transdisciplinary teams of scientists to accelerate progress toward reducing cancer incidence, morbidity, and mortality associated with obesity, low levels of physical activity, and poor diet. This program is part of the NCI's larger energy balance research focus, complementing the trans-NIH Obesity Task Force.
- Biostatistical Modeling to Evaluate Cancer Control Interventions. Cancer Intervention and Surveillance Modeling Network (CISNET) is a consortium of NCI-sponsored teams who use biostatistical modeling to improve our understanding of cancer control interventions in prevention, screening, and treatment. The teams use data from randomized controlled trials, meta-analyses, observational studies, national surveys, and studies of practice patterns to evaluate the past and potential future impact of these interventions. Currently CISNET has teams focusing on breast, prostate, colorectal, and lung cancers.
- Linking Science and Technology. Nanotechnology Alliance for Cancer has begun harnessing nanotechnologies for cancer diagnostics, targeted imaging, and drug delivery. Multifunctional, targeted devices capable of bypassing biological barriers will enhance our ability to treat cancer effectively and efficiently by delivering therapeutic agents directly to cancer cells.
- Sharing Information to Advance Cancer Research. The caBIG™ (cancer Biomedical Informatics Grid™) initiative was launched to connect scientists and practitioners through a shareable and interoperable infrastructure that has standard rules and a common language to more easily share information. caBIG™ will build or adapt tools for collecting, analyzing, integrating, and disseminating information associated with cancer research and care.
- Using the Genome Map to Advance our Understanding of Cancer. The Cancer Genome Atlas (TCGA) is a pilot project to assess the feasibility of a full-scale effort to systematically identify all genetic changes involved in human cancer. Tumors to be studied are lung, brain (glioblastoma), and ovarian. All data will be publicly available to researchers worldwide through caBIG™.

NCI educates cancer patients, health and research professionals, and the public about women's health and cancer research in a variety of formats. Information is provided to the public, the cancer community, and journalists through the NCI Web site, http://www.cancer.gov. The NCI's Research on Cancers in Women page provides highlights of NCI-supported research to understand, prevent, diagnose, and treat cancers in women, http://women.cancer.gov.

Cancer information is also provided through staffed NCI exhibits at key conferences, meetings, and events. The NCI Cancer Information Service (CIS) shares information about cancer prevention, risk factors, symptoms, diagnosis, treatment, research, and quitting smoking. CIS information specialists provide the latest, most accurate information about cancer by telephone (1-800-4-CANCER), TTY (1-800-332-8612) and on the Internet through *LiveHelp* instant messaging service on NCI's Web site (http://cancer.gov).

CIS also provides printed and electronic NCI publications through the NCI Pubs Locator https://cissecure.nci.nih.gov/ncipubs/ or by calling 1-800-4-CANCER. Through its Partnership Program, CIS works with established national, regional, and state partner organizations to reach and educate minority and medically underserved women with limited access to health and cancer information.

The following sections describe research activities and accomplishments across the cancer continuum related to specific cancers.

BREAST CANCER

Although advances in prevention, detection, diagnosis, and treatment are having a beneficial impact on breast cancer incidence, mortality, and survival, this disease continues to have a devastating impact on American women. By the end of 2007, an estimated 178,480 women are expected to be diagnosed with invasive breast cancer and 62,030 with *in situ* breast cancer; an estimated 40,460 women will have died of the disease. More than 2.3 million women in the United States have either survived breast cancer or are living with breast cancer today. Breast cancer is responsible for the highest number of new, invasive cancer cases among women each year and, in women, is the second leading cause of cancer deaths, after lung cancer. Following long-term increases, breast cancer incidence rates for women had a non-significant decrease from 2001 through 2003. Overall, there was a 6 percent relative decline in breast cancer incidence between 2002 and 2003. There was a 14 percent decrease in incidence rates among women aged 50-69 diagnosed with estrogen receptor positive breast cancer, which may have been due to the recent decline in use of hormone replacement therapy (HRT) by postmenopausal women. Death rates from breast cancer for all women began decreasing in the early 1990s, although the differential in mortality among racial/ethnic populations is widening. While breast cancer survival rates have improved by about 14 percent since the mid 1970s, this progress is not impacting all populations equally. Even when controlled for age and stage at diagnosis, breast cancer mortality rates vary greatly among racial/ethnic populations. The highest rates are seen in Black women, followed by non-Hispanic White and Hispanic women. Rates are lowest in Asian Pacific Islanders (APIs) and American Indians/Alaskan Natives.

Breast Cancer Specialized Programs of Research Excellence (SPOREs). Ten breast cancer SPORES (http://spores.nci.nih.gov/current/breast/breast.html) conduct collaborative, multidisciplinary research to develop novel agents and technologies for breast cancer treatment and prevention and to identify biomarkers for diagnosis, prognosis, screening, prevention, and targeted treatments. For example SPORE researchers have shown that three tests, now in clinical testing, that use gene expression patterns to predict breast cancer outcomes appear to be more predictive than traditional pathological data, such as tumor size and grade.

BIOLOGY AND GENETICS

Biology of Normal Breast Tissue. A better understanding of the biology of normal breast tissue will help researchers to identify early molecular changes that lead to cancer and to develop more effective prevention, early detection, and treatment strategies. For example, research suggests that breast cancers arise from a population of stem cells that are present in the normal mammary gland. Researchers are studying these breast stem cells to determine what events may initiate the tumorigenic process. Researchers also have developed comprehensive methods using ductal lavage and ductal endoscopy with endoscopic sampling to evaluate high-risk breast duct and ductal epithelium.

Trans-NCI Breast Premalignancy Program. NCI has initiated this unique program using proceeds of special-issue U.S. postal stamps mandated by the Stamp Out Breast Cancer Act. This comprehensive program in breast cancer premalignancy encompasses prevention, etiology, biology, diagnosis, and molecular epidemiology research. Researchers investigating the molecular epidemiology and biology of mammographic density, the biology of breast premalignancy and tumor stem cells, decision-making approaches to chemotherapy, strategies for early detection, and nano-imaging technologies.

Mouse Models. In 2005 and 2006, researchers from the NCI Mouse Models of Human Cancers Consortium (NCI-MMHCC; http://emice.nci.nih.gov/) developed and used mouse models to better understand breast cancer development and progression. For example, researchers derived a series of mouse models that reproducibly represent the progression of breast cancer from ductal carcinoma in situ (DCIS) to invasive malignancy. These models show that the major molecular and genetic changes required for metastasis are already present at the earliest stages in breast cancer lesions that eventually metastasize. This research also shows that changes that lead to cancer

and its progression can be subtle and inconsistent. A transgenic model of preneoplastic progression of breast cancer has been used to show that inflammatory cells play a critical role in mediating proliferation of breast epithelial cells and neo-vascularization. Small animal imaging allows exploration of functional changes as breast cancer develops and metastasizes, and investigation of the tumor micro-environment and its role in metastasis. NCI-MMHCC collaborations with epidemiologists have facilitated the discovery of four new common polymorphic human susceptibility genes, which were identified in mice and then assessed in human breast cancers.

HER2 , AIB1, mTOR. About 30 percent of human breast cancers show overexpression of the protein *HER2.* These tumors are aggressive with a high rate of relapse and poor prognosis. Previous research has found Herceptin® (trastuzumab) therapy, which targets HER2, to slow disease progression in about one third of patients with HER2-positive breast cancer, although these patients eventually develop resistance to the drug. Preclinical research continues to inform efforts to improve treatment efficacy in patients with HER2-positive tumors. One study suggests that inhibition of HER2 binding to the protein alpha-6-beta-4 may help combat resistance to HER2-targeted therapy. Another study has implicated the mTOR pathway in HER2 positive tumors that also overexpress the protein AIB1. Investigators suggest that tumors positive for HER2 and AIB1 may be more effectively treated with an ER inhibitor, such as tamoxifen in combination with an inhibitor of the mTOR pathway.

Brain Metastasis. Studies Directed Toward the Eradication of Brain Metastases of Breast Cancer is a multi-institutional consortium, supported by a U.S. Department of Defense Breast Cancer Research Program Center of Excellence and led by NCI scientists. Studies focus on the mechanistic underpinnings of brain metastases and provide preclinical data to advance compounds to clinical trial for this devastating complication.

Cohort Studies. The NCI Consortium of Cohorts addresses the need for large-scale collaborations for the study of gene-gene and gene-environment interactions in the etiology of cancer. The Breast and Prostate Cancer Cohort Consortium includes ten cohorts with pooled data from 6,160 patients with breast cancer. Researchers will analyze common variations in about 50 candidate genes involved in steroid hormone metabolism and insulin-like growth factor signaling pathways for association with cancer risk. Another cohort study, The Cancer Genetic Markers of Susceptibility Project, is conducting scans of the entire human genome to identify common, inherited gene variants that increase the risk of breast cancer.

Specimen Resources. The Cooperative Breast Cancer Tissue Resource Database (http://www-cbctr.ims.nci.nih.gov/) is a Web-based "virtual tissue bank" with a central database to track each tissue in the system. Researchers can search this database online and obtain tissues with associated clinical information. The resource has recently begun to provide tissue microarrays to researchers studying molecular signatures of breast cancer.

RISK FACTORS

Genetic Factors

Breast Cancer Susceptibility Mutations. NCI scientist have confirmed reports that approximately one in every 200 U.S. women carries a *CHEK2* gene that almost doubles the risk of developing breast cancer compared to women without the mutation. Another study estimates that certain mutations in a gene *BRIP1* associated with Fanconi anemia, may double breast cancer risk. Mutations in *CHEK2*, *BRIP1,* and a third gene, *ATM*, appear to predispose a woman to cancer only in the presence of other genetic or environmental risk factors.

DNA Repair Capacity. A study supported through the NCI Breast Cancer Family Registry suggests that DNA repair capacity may be a valuable "*in vitro"* biomarker to identify women at high risk for breast cancer, especially in familial breast cancer families. Lymphoblastoid cells of breast cancer patients were less effective than cells from their healthy sisters in responding to an *in vitro* chemical mutagenic assault, especially in women younger than 40.

The relative risk of breast cancer was nearly three times greater between the groups with the most and the least DNA repair capabilities.

Reproductive Factors. There is well established evidence for an association between decreased breast cancer risk and early age at first term birth, increasing parity, and long duration of lactation. Breast cancer risk is temporarily increased for several years following pregnancy. However, no association has been found between increased breast cancer risk and either spontaneous or induced abortions. Other reproductive factors associated with increased risk of developing breast cancer include early age of first menstrual period, late age of menopause, and use of menopausal hormone replacement drugs.

Diet. The NCI-sponsored Women's Intervention Nutrition Study was the first large-scale study to examine the influence of dietary fat on breast cancer outcomes in postmenopausal women treated for early-stage breast cancer. After 5 years, women on the low-fat diet showed a significant reduction in cancer recurrence compared with the control group: 9.8 percent vs. 12.4 percent. Women on the low-fat diet who had been previously treated for non-estrogen-dependent cancer – which is typically associated with a greater likelihood of recurrence – had a 42 percent reduced risk of recurrence compared with those on a standard diet.

The NCI sponsored a scientific workshop in March 2006, *Feasibility of a Physical Activity, Weight Control Trial to Prevent Breast Cancer*. Workshop participants reviewed evidence to debate the feasibility, utility, and design issues for a possible clinical trial and to identify research gaps and opportunities to advance the field. A scientific report and planning for next steps are in progress.

NCI is sponsoring the Women's Healthy Eating and Living (WHEL) Study, a multi-site randomized controlled trial of the effectiveness of a high-vegetable, low-fat diet on reducing additional breast cancer events and early death in women with early-stage invasive breast cancer. Follow up of the 3,088 study participants will continue through 2006 and reports of primary outcomes are expected in 2007.

Hormones. NCI-supported research is helping to clarify the effects of various hormones on breast cancer risk. In 2002, the Women's Health Initiative (WHI) published results of the Estrogen-Plus-Progestin Study, which found an increase in breast cancer in women taking combined hormone therapy. According to a new analysis of NCI Surveillance, Epidemiology, and End Results (SEER) data, breast cancer incidence in the United States dropped sharply by 7 percent between 2002 and 2003. A decline of 14 percent was found in women between ages 50-69 diagnosed with ER positive breast cancer. Researchers suggest that this drop may be associated with the reduction in use of hormone therapy by postmenopausal women. Other research has revealed an association of *in utero* exposure to diethylstilbestrol (DES), a synthetic estrogen, and risk of adult breast cancer. Among a cohort of exposed and unexposed women followed since the 1970s, DES exposure was associated with an increased breast cancer risk among women aged 40 and older. Researchers will continue surveillance of this cohort.

Preclinical researchers investigating 2-methoxyestradiol (2ME2) found a paradoxical effect of this hormone on cancer risk. Although 2ME2 significantly reduced tumor growth at late stages, the data suggest that altered tumor morphology and accelerated tumor growth may occur if the hormone is administered in a prevention setting for prolonged periods.

Other Studies of Environmental and Lifestyle Risks. Although much of the research of the Long Island Breast Cancer Study Project (LIBCSP) is complete and no association was found between residential electromagnetic fields and increased risk for breast cancer, further analyses and a follow-up study are in progress. Current research is aimed at defining breast cancer risk associated with environmental and lifestyle factors including studies of regional differences in breast cancer rates in the United States; prenatal-to-adult environmental exposures potentially leading to breast cancer; possible relationships between Dichloro-Diphenyl-Trichloroethane (DDT) exposure and breast cancer risk, benign breast cancer conditions, and other outcomes among women; the effects of

lifetime radiation on breast cancer risk; and the role of residential distance from steel mills, chemical factories, toxic waste sites, and other industries as risk factors for breast cancer. NCI also cofunds four Breast Cancer and Environment Research Centers (BCERC; http://www.bcerc.org/) with the National Institute of Environmental Health Sciences (NIEHS) to study the impact of prenatal-to-adult environmental exposures that may predispose a woman to breast cancer.

Cancer Family Registries. The Cancer Family Registries (http://epi.grants.cancer.gov/CFR/) is an international registry system available to researchers who are planning to conduct population- and clinic-based interdisciplinary research with a main focus on the genetic and molecular epidemiology of breast, ovarian, and colorectal cancers.

PREVENTION

Chemoprevention. The Study of Tamoxifen and Raloxifene (STAR: http://www.cancer.gov/star) compared these two selective estrogen receptor modulators (SERMs) for reducing the incidence of breast cancer in postmenopausal women at increased risk for the disease. One of the largest breast cancer prevention studies ever, STAR took place at more than 500 centers across the United States, Canada, and Puerto Rico. Initial results, released in April 2006, show that raloxifene is as effective as tamoxifen in reducing the breast cancer risk of trial participants: both drugs reduced the risk of developing invasive breast cancer by about 50 percent. In addition, women taking raloxifene had 36 percent fewer uterine cancers and 29 percent fewer blood clots over a period of about 4 years than the women who were taking tamoxifen.

Other chemoprevention research Breast cancer clinical trials are ongoing to test for preventive properties of the isoflavone genistein, the statin Simvastin, the selective rexinoid compound bexarotene, the non-steroidal anti-inflammatory drug (NSAID) sulindac, and grape seed proanthocyanidin extract. NCI is also supporting investigator-initiated research to identify potential molecular targets for prevention of human ER negative breast cancer.

Prophylactic Mastectomy. Cancer Research Network (CRN) investigators have reported that, in patients with cancer in one breast, contralateral prophylactic mastectomy reduced the risk of death from breast cancer by 43 percent after an average of 5 years of follow-up. A related CRN study found that, among women at elevated risk for breast cancer, less than 1 percent of women who received prophylactic mastectomy subsequently developed breast cancer, compared to 4 percent of women who did not undergo the surgery. Furthermore, recent research shows that prophylactic mastectomy in women with *BRCA1* or *BRCA2* mutations reduces risk of breast cancer by about 90 percent. Further research on potential physical and psychological harms of prophylactic mastectomy is needed.

Prophylactic Oophorectomy. A recent study of 1,439 patients with breast cancer and 1,866 matched controls found that a previous history of oophorectomy was associated with a significant reduction in breast cancer risk of 56 percent for *BRCA1* carriers and of 46 percent for *BRCA2* carriers. The benefit was greatest in women who had an oophorectomy before age 40 and the protective effect was evident for 15 years post-oophorectomy.

Physical Activity. Researchers are investigating the preventative effects of physical activity in women at high risk for, or with a history of, breast cancer.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Imaging Technologies for Breast Cancer Screening

Mammography NCI invests in research to improve the efficacy and use of mammography. The Breast Cancer Surveillance Consortium (BCSC), http://breastscreening.cancer.gov/index.html, studies breast cancer screening practices and fosters collaborative research to improve the practice of community-based mammography screening. Recent BCSC research found that inclusion of breast density in the Gail Model, an interactive model to predict breast cancer risk, improved prediction accuracy for both pre- and post-menopausal women. Another BCSC study

has reported that inadequate use of screening mammography may be an important reason why Black women are more likely to be diagnosed with advanced stage breast cancer than women of other ethnic groups.

In 2006, NCI and the American Cancer Society (ACS) began an initiative for "Assessing and Improving Radiologists' Mammography Interpretive Skills." This project will examine factors that influence accuracy in the interpretation of mammograms to improve training and skill maintenance of interpreting physicians. An initial study has established a baseline of performance by radiologists from several facilities across the United States. Another study reported that the number of radiologists appropriately recommending a short-interval follow-up (usually 6 months) increased from 51 percent in 1996 to 76 percent in 2001.

The NCI-supported American College of Radiology Imaging Network (ACRIN) Digital Mammography Imaging Screening Trial (DMIST: http://www.cancer.gov/dmist) compared the efficacy of digital mammography and film-based mammography. Investigators reported that women with dense breasts, who are pre- or perimenopausal, or who are younger than age 50, would benefit from having a digital rather than a film mammogram. Analyses of reader variability and cost-benefit are in progress.

Effectiveness of Mammography A group of investigators used SEER data to identify any geographic association between the level of use of breast cancer screening and breast cancer mortality. Analyses suggested a moderate effect of mammography use on decreasing breast cancer mortality in the United States, which seems to support the conclusions of randomized mammographic screening trials.

Other Imaging Technologies NCI is funding research on a variety of other technologies for breast imaging, including magnetic resonance imaging (MRI), ultrasound, magnetic resonance spectroscopy, computer-aided diagnosis, elastography, positron emission tomography (PET), single photon emission computed tomography (SPECT), and thermography. Selected studies seek to improve screening techniques for women with dense breast tissue and for women with BRCA mutations. For example, the Screening Breast Ultrasound in High-Risk Women Study, is designed to assess the effectiveness of whole breast bilateral screening sonography combined with mammography, compared to mammography alone for detection of breast cancer in women with dense breasts. Results from a completed clinical trial to assess the performance and usefulness of high resolution MRI to detect contralateral disease in women with breast cancer is expected in early 2007.

Prognosis. The Trial Assigning Individualized Options for Treatment (Rx) (TAILORx) aims to use the Oncotype DX™ assay to determine the most appropriate therapy with the fewest side effects for patients with early stage breast cancer. Onco*type* DX™ is a diagnostic tool developed by Genomic Health, Inc., in collaboration with the National Surgical Adjuvant Breast and Bowel Project (NSABP). This tool quantifies the likelihood of disease recurrence in women with early stage breast cancer and assesses the likely benefit from certain types of chemotherapy.

Investigators searching for novel genetic prognostic markers for breast cancer recently found an association between polymorphisms in the gene *SIPA1* and poor outcome in women with this disease. Another study found that prediction of breast cancer outcome by tumor p53 status is dependent on a mutation in the *MDM2* oncogene. Researchers are also studying gene signatures to identify highly aggressive and less aggressive cancers. Investigators have demonstrated an inherited susceptibility to the development of visceral metastases in patients with breast cancer. Further evidence suggests that the genetic factors responsible for inherited risk for metastases may significantly contribute to the characteristic gene expression profiles that predict lung metastasis. This cutting-edge research could lead to novel prognostic markers to aid health care providers in patient management and may provide targets for new drug development.

Anti-hormone Adjuvant Therapy. Researchers are exploring ways to improve and extend the effectiveness of tamoxifen therapy, understand drug interactions, combat tamoxifen resistance, and identify alternative therapies for breast cancer. Current regimens of tamoxifen treatments are effective for 5 years, after which tumors develop resistance to the drug. Researchers have shown that small dosages of disulfide benzamide (DIBA) compounds can reverse tamoxifen resistance in human breast carcinoma cell lines and in *in vitro* and *in vivo* xenograft models. This is the first report of the ability to reverse tamoxifen resistance.

A new SPORE study has shown that some women taking tamoxifen may not receive the intended benefit due to genetic differences in the way tamoxifen is metabolized. Genetic polymorphisms and many commonly administered drugs, such as selective serotonin reuptake inhibitors, can affect the activity of an enzyme called cytochrome CYP2D6, which has been shown to activate tamoxifen's therapeutic effect. Women with factors that impaired CYP2D6 metabolism had significantly shorter time to disease recurrence and worse disease-free survival compared with women who metabolized the drug normally.

Aromatase inhibitors (AIs) are compounds that suppress estrogen levels by inhibiting an enzyme necessary for estrogen production. A meta-analysis* that combined data from three randomized clinical trials suggests that, for postmenopausal women with hormone-sensitive early-stage breast cancer, switching to the AI, Arimidex® (anastrozole) after 2 to 3 years on tamoxifen significantly reduced the occurrence of contralateral breast cancer.

Other clinical studies are assessing anastrozole versus tamoxifen for adjuvant treatment of ductal carcinoma *in situ;* investigating anastrozole with or without fulvestrant (Faslodex®) as a first line therapy in postmenopausal women with metastatic breast disease; and comparing the safety, acceptability, and side effects of letrozole (Femara ®) versus placebo in postmenopausal women at increased risk for breast cancer recurrence.

Conventional Chemotherapies

Age effects Research has shown that post-operative chemotherapy can improve outcomes in women diagnosed with estrogen receptor-negative, node-negative breast cancer. More recently, NSABP investigators reported that benefits from post-operative chemotherapy with either cyclophosphamide plus methotrexate and 5-fluorouracil or doxorubicin with cyclophosphamide were greater, the younger the age of the patient. Also, the recurrence-free survival benefit was greater for pre-menopausal women. However, another study* showed that, although women over age 65 experience more treatment-related mortality, the benefits of disease-free and overall survival were similar for older and younger women who received adjuvant chemotherapy.

Effectiveness of Differing Treatment Regimen NCI is sponsoring a clinical trial for breast cancer treatment to compare the effectiveness of four different treatment schedules using the drugs doxorubicin, cyclophosphamide, and taxane therapy in treating patients who have undergone surgery for breast cancer. Preliminary results show that no one schedule was more effective than another. Results from a secondary analysis are expected in 2007.

Molecularly Targeted Therapy. NCI supports preclinical research to identify potential molecular targets for cancer therapy. Investigators recently found that Gleevec™ invokes tumor regression in mammary tumors of a mouse model with high levels of c-kit expression. A study using a different mouse model found that the proteasome inhibitor, bortezomib (Velcade®), significantly sensitizes certain human tumor cells to tumor necrosis factor-α-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis. The combination of these two agents appeared to be superior to either agent alone. Medroxyprogesterone acetate, a progestin that has been tested as a treatment for advanced breast cancer has been found to elevate expression of the Nm23-H1 metastasis suppressor gene in

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hormone receptor-negative metastatic human breast carcinoma cell lines, thereby reducing metastatic colonization. This indicates a possible treatment benefit for the subset of patients with hormone receptor-negative breast cancer.

Radiation Therapy. Researchers report* that patients with high-risk breast cancer treated with radical mastectomy and adjuvant chemotherapy were more likely to survive if they also had localized radiation treatment. NCI is conducting a clinical trial of partial-breast irradiation to test whether this technique is equivalent to irradiation treatment of the whole breast.

Monoclonal Antibodies. In 2006, the Food and Drug Administration (FDA) expanded the approved use of Herceptin®, a monoclonal antibody that binds to HER2, for the treatment of HER2-positive breast cancer after lumpectomy or mastectomy. Two studies leading to this approval were conducted by NCI-sponsored Cooperative Groups. The studies closed early after showing that women who received Herceptin combined with chemotherapy had 53 percent fewer relapses and a significant improvement in overall survival for up to 3 years after surgery. Herceptin is also FDA approved for treatment of metastatic breast cancer.

Preliminary clinical trial results reveal that the antiangiogenesis drug, bevacizumab (Avastin®) can slow progression of recurrent or metastatic breast cancer when it is combined with the chemotherapy drug, paclitaxel (Taxol). Avastin is already approved by FDA to treat colorectal cancer when combined with chemotherapy. In other work, NCI researchers are developing potential breast cancer treatment strategies that use monoclonal antibodies to target apoptosis-inducing death receptors located on cancer cells.

Novel Compounds. Researchers supported by NCI preclinical research programs are helping to develop novel compounds that may be effective for breast cancer treatment. For example, compounds under investigation inhibit various kinases, tumor growth factors, prostaglandins, or angiogenesis factors; cause histone deacylation, immune activation; or are microtubule agents.

Treatment Monitoring. NCI supports research to explore the uses of imaging to monitor therapy. One study is examining use of dynamic contrast enhanced MRI to monitor the effects of Avastin on anti-angiogenesis and the use of optical imaging for sentinel node detection. Investigators also have developed a molecular probe for *in vivo* PET monitoring of HER2 expression. A clinical trial is using contrast-enhanced MRI to identify molecular and imaging characteristics for selection of patients most likely to respond to novel therapies that could be tested prior to or with standard therapies

Adverse Effects. Two new studies suggest that women receiving certain breast cancer treatments should have their cardiac health monitored. One study reported that long-term Herceptin use appears to be safe, but that some patients will develop cardiac toxicity. The second study reported that irradiation of the left breast was not associated with an increased mortality from cardiac disease for up to 20 years after treatment, but was associated with a higher rate of coronary artery disease and myocardial infarction compared with treatment of the right breast.

One of the more troubling adverse treatment effects of breast cancer is lymphedema. A team of researchers is evaluating the use of strength training as a means to prevent this disorder in patients treated for breast cancer. A second study is investigating the risk factors, development, progression, regression, and fluctuations of lymphedema, as well assessing quality of life measures.

CANCER CONTROL, SURVIVORSHIP, AND OUTCOMES RESEARCH

Education and Outreach. NCI supports research to discover better ways of communicating information about breast cancer. Researchers funded by NCI and the Agency for Health Care Research and Quality are studying how

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to communicate benefits and limitations of breast cancer screening tests; developing tools to help women ask themselves important questions and make informed decisions about screening; and exploring new communication technologies, including online and other interactive health communications tools to address women's concerns. The NCI Centers of Excellence in Cancer Communications Research (CECCR) includes research exploring ways of communicating risk about tamoxifen prophylaxis to women at high risk for breast cancer.

NCI also works with partners to develop and distribute accurate and timely information on breast cancer and other important cancer-related health messages. In 2005, the Department of Health and Human Services and NCI launched a consolidated Department-wide information source on breast cancer in one Web site (http://www.hhs.gov/breastcancer). Other resources include a new, free educational video, *Moving Beyond Breast Cancer,* for women finishing breast cancer treatment. The 23 minute video features vignettes of women in different life stages who share their concerns and experiences. In 2005, producers for CBS-TV's *As the World Turns* soap opera developed two story lines with scientific feedback from NCI. One involved a main character with breast cancer and another involved a pregnant teen who smokes. Public service announcements, featuring stars from the shows, addressed mammography and teen smoking and pregnancy.

Improving Use of Screening. Investigators tested the effect of lay health advisor (LHA) intervention on mammography use by low income women in a triracial, rural population in North Carolina. At follow-up, the women in the LHA group had significantly better belief scores, reduced barriers to follow up, and were more likely to have received a mammogram than women in the comparison group. In a study based in New York City, women in underserved communities who were contacted by trained counselors by phone had higher screening rates for mammography, Papanicolaou (Pap) testing, and colon cancer testing.

Improving Quality of Care. The NCI Center to Reduce Cancer Health Disparities (CRCHD) is administering development of an innovative Patient Navigator Research Program (http://crchd.cancer.gov/pnp/pnrp-index.html), focusing on four cancers for which screening tests are available: breast, cervical, prostate and colorectal. Patient navigators are trained, culturally sensitive health care workers who provide support and guidance throughout the cancer care continuum. Eight participating research institutions will provide navigators to help patients and their families manage cancer diagnoses and overcome common barriers to obtaining timely and appropriate cancer care and treatment.

Survivorship Research. NCI reissued the Long Term Cancer Survivors Research Initiative in 2005. This research addresses the full range of domains affected by cancer and its treatment (physical, psychosocial, behavioral, and economic) in long-term survivors. The initiative focuses on understudied areas and gaps in research.

Bone Fracture Risk Researchers from the WHI Observational Study followed a cohort of breast cancer survivors for 5.1 years and monitored for first-event bone fractures. Compared with a reference group of women, those who had been treated for breast cancer reported a higher incidence of bone fractures.

HEALTH DISPARITIES

While White women have the highest rate of breast cancer incidence, Black women have the highest death rate of all races from the disease. *NCI's Annual Report to the Nation on the Status of Cancer 1975-2003, With a Special Feature on Cancer Among U.S. Hispanic/Latino Populations* reported that Latinos have lower incidence rates than non-Hispanic whites (NHW) for breast cancers, but are less likely than the NHW population to be diagnosed with localized stage cancers. A recent study retrospectively analyzed data from women who had been treated with mastectomy and either adjuvant or neoadjuvant systemic therapy at the M.D. Anderson Cancer Center between 1975 and 2000. The study found that, among women receiving the same treatment regimen, Black women were more likely to have larger, later stage tumors and lower survival rates than Hispanic and White women. Research is needed to determine how to improve outcomes for Black patients by understanding and addressing tumor biology.

Disparities in Care. A study using SEER data, as well as clinical and administrative databases, concluded that age is an independent risk factor for receipt of non-standard cancer therapies. The investigators found that women aged 75 and older were more likely to receive nonstandard primary tumor therapy than younger women. Additionally, Black women were less likely to be prescribed tamoxifen and Asian women were more likely to undergo breast conserving surgery than were White women. Another study found that use of evidence-based treatment guidelines were significantly lower for patients who depend on Medicare or Medicaid alone for insurance. Black patients with Medicare were the least likely to receive recommended therapy.

Biologic Factors. Researchers seek to identify potential biological factors contributing to the lower breast cancer incidence rates coupled with higher breast cancer mortality rates observed in Black women compared with corresponding rates observed in White women. Research includes studies to understand hormonally nonresponsive breast cancers, including ER positive and epidermal growth factor receptor (EGFR) overexpressing breast cancers in Black women.

CERVICAL CANCER

An estimated 11,150 cases of invasive cervical cancer are expected to be diagnosed in the United States in 2007 and 3,670 women are expected to die from the disease. Incidence and mortality rates have decreased steadily over the past five decades, largely due to the widespread use of the Pap smear which detects cervical cancer and pre-cancerous lesions. The Pap smear has made cervical cancer one of the most preventable cancers, but older, poorer, and less educated women are less likely to be screened and screening is not available in many low-resource regions of the world. Worldwide, cervical cancer has a significant impact, with nearly 500,000 new cases and nearly 250,000 deaths reported annually.

Cervical Cancer SPORE. The SPORE for cervical cancer research, located at the Johns Hopkins University School of Medicine, focuses on developing better screening, prevention, and therapeutic tools. This SPORE has a screening project in rural India and multiple interactions with the NCI Rapid Access to Intervention Development (RAID) and Intramural Programs, as well as outside companies, foundations and universities, for the development and testing of novel therapeutic and preventative agents.

RISK FACTORS

Human Papillomavirus (HPV). Although oncogenic HPV infections are common and usually clear within 1 to 2 years, infection with certain HPV subtypes is now recognized as the major cause of cervical cancer. A group of approximately 15 HPVs cause virtually all cases of cervical cancer worldwide, with HPV types 16 and 18 accounting for approximately 70 percent of all cases.

Investigators have identified a possible link between immune response and development of cervical cancer. They showed that combinations of mutations in two genes associated with immune response, *HLA* and *KIR*, may influence a women's susceptibility to developing precancerous lesions after HPV infection. Mutation combinations that appeared to confer resistance to lesion development were associated with inhibition of natural killer (NK) cell activity. Combinations that seemed to confer susceptibility were associated with activation of NK cells. Further research is needed to investigate the role of the inflammatory process and NK cells in the development of cervical cancer.

NCI is supporting large, population-based cohort studies, including the Guanacaste Study of HPV Natural History in Costa Rica and the Portland Kaiser Permanente cohort study in the United States, to better define risk factors for progression of precancerous lesions among HPV infected women. The Costa Rican study will assess the various roles of mucosal immune response, HLA alleles, chromosomal alterations, contraceptive and reproductive practices, diet, cigarette smoking, and infection with sexually transmitted agents other than HPV. The U.S. study is investigating specific immune responses to viral infection and risk of persistence and/or progression of lesions. Researchers will test *in vitro* biological specimens for immunological markers that may correlate with disease status over time.

Biomarkers of Risk. The Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED) will comprehensively identify and validate biomarkers for each progressive stage of cervical neoplasia (normal, HPV-infected, precancer, cancer). The investigators hope to develop a new set of biomarkers that can distinguish women at highest risk of cervical cancer from those with benign HPV infection.

DES. NCI continues to follow cohorts of women and their offspring exposed to DES during pregnancy. So far, analyses show no excess risk of cancer overall in DES-exposed offspring, compared with levels of risk for the general population, as calculated from SEER data. Data from the Third Generation Study, which is assessing DES-related cancer risk in women whose mothers were exposed to DES *in utero*, show no effects of DES on age at menarche or menstrual irregularity. NCI provides online information to DES references at http://www.cancer.gov/cancertopics/des

Rare Cervical Carcinomas. The risk factors for development of rare forms of cervical cancer, such as adenocarcinoma and adenosquamous carcinoma, are not as well defined as for the more common squamous cell carcinoma. The multi-center Cervical Adenocarcinoma Case-Control Study is examining the role of potential risk factors for development of rare histological forms of cervical cancer. A total of 595 women have responded to a detailed risk factor questionnaire and had blood and cervical specimens collected for HPV testing and other bioassays of interest. Another recent study* shows that HPV infection is a risk factor for development of cervical adenocarcinoma.

PREVENTION

HPV Vaccine. NCI and partners are designing vaccines to prevent cervical cancer by protecting women against persistent HPV infection. In June 2006, the FDA approved the use of a new vaccine, Gardasil™, made by Merck & Co., Inc. which targets four HPV types: 6, 11, 16 and 18. For women who had no evidence of previous infection, the vaccine was 100 percent protective against development of persistent infection or cervical abnormalities associated with HPV 16 or 18, and protected against genital warts caused by HPV 6 and 11. The vaccine is based on laboratory research and technology developed at NCI.

NCI is conducting a randomized, controlled phase III trial of a vaccine developed by Glaxo-Smith-Kline to prevent HPV16 and 18 infections and their associated cervical lesions. The vaccine is based on virus-like particle technology developed by NCI intramural investigators. Recruitment is complete and the trial is underway in an area of Costa Rica with exceptionally high rates of cervical cancer. The trial will also evaluate potential prophylactic protection against other HPV subtypes, possible therapeutic effect in women previously infected with HPV, vaccine durability, underlying biological/immunological mechanisms of protection, and other important public health issues.

Condom Use. A small prospective study* showed that, in women new to sexual intercourse, those who used condoms 100 percent of the time were 70 percent less likely to develop HPV infection than women who used condoms less than 5 percent of the time.

Carrageenan. Another group of researchers discovered that carrageenan, a compound found in a variety of food products, cosmetics, and sexual lubricants, is a potent genital HPV infection inhibitor. If proven safe and effective in a clinical trial, sexual lubricants containing carrageenan could complement the recently approved HPV vaccine by preventing infection by HPV subtypes not targeted by the vaccine.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

The ASCUS-LSIL Triage Study (ALTS). Research funded by NCI and others has demonstrated that detection of DNA from HPV16 and HPV18 predicts increased risk of cervical precancers and cancers that may develop up to several years following testing. The NCI-funded ALTS, http://www.cancer.gov/prevention/alts/index.html, investigated the clinical management of low grade cervical cytologic abnormalities. The findings showed that HPV DNA testing can be used to triage patients diagnosed with ASCUS (atypical squamous cells of undetermined significance), but not LSIL (low-grade squamous intra-epithelial lesions). HPV DNA negativity after ASCUS diagnosis implies very low risk of cervical precancer or cancer. The study found that a single colposcopy with biopsy, although previously considered the gold-standard for diagnosis, detected only about two-thirds of high grade lesions. Increasing the number of biopsies increased the sensitivity of the procedure. The ALTS Immunology Study is prospectively identifying biomarkers associated with a permissive versus protective immune response to low-grade cervical lesions.

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Human Telomerase Gene (*TERC*) Investigators have found that amplification of *TERC* is a consistent aberration in cervical adenocarcinomas and may provide an objective genetic test for the assessment of glandular cells in Pap smears and hence the diagnosis of this rare form of cervical cancer. Other research has shown that an assay to detect genomic amplification of *TERC* in Pap smears predicts the development of cervical cancer from early to later stage lesions.

TREATMENT

Chemotherapy. In 2006, the FDA approved use of topotecan hydrochloride (Hycamtin®) in combination with cisplatin for treatment of late-stage cervical cancer for women in whom surgery or radiation therapy is not likely to be effective. In clinical trials, this treatment improved survival from about 6.5 to 9.4 months, but had serious side effects, including a drop in white blood cells and platelets. Topotecan hydrochloride was already approved for treatment of ovarian and small-cell lung cancers.

Treatment-Related Side Effects. Researchers are testing interventions to alleviate or prevent side effects of cervical cancer treatment, including treatment-induced anemia and quality of life changes.

CANCER CONTROL, SURVIVORSHIP, AND OUTCOMES RESEARCH

Communication. A recent analysis of responses to the Health Information National Trends Survey (HINTS) showed that only 40 percent of respondents had heard of HPV and less than half of those were aware of the virus' connection to cervical cancer. Awareness was lowest among women who were older, less educated, or less exposed to health information. The researchers note that consistent information about HPV, its link to cervical cancer, and how to prevent and detect it, needs to be provided before a woman becomes infected.

Psychosocial Issues. The NCI-funded Center for Psycho-Oncology Research conducts behavioral, psychological, social, and biomedical research on the interrelationships between cognition, emotion, biological processes, and physical health in patients affected by cancer, including women at high risk for cervical cancer due to co-infection with HIV (human immunodeficiency virus) and HPV. An NCI-supported study is looking at behavioral and immunologic components that correlate with 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 assess sexual function and general quality of life for women receiving treatment for different stages of cervical cancer. NCI is supporting about a dozen studies that address the social, emotional, and interpersonal impact of cancer and its treatment on sexual functioning in survivors and their partners. This research will provide information on how best to counsel survivors and their partners on what to expect after treatment and ways to minimize some of the more distressing personal costs of disease treatment and cure.

HEALTH DISPARITIES

Access to Health Care and Screening. The NCI CRCHD has an ongoing program to address the entrenched pattern of high cervical cancer mortality found in distinct U.S. populations and geographic areas. Women most affected include Black women in the South, Latino women along the Texas-Mexico border, White women in Appalachia, American Indians of the Northern Plains, Vietnamese-American women, and Alaska Natives. In 2005, the CRCHD released the report, *Excess Cervical Cancer Mortality: A Marker for Low Access to Health Care in Poor Communities* (http://crchd.cancer.gov/attachments/excess-cervcanmort.pdf). The authors propose intensifying outreach to underserved women, stressing the importance of a "medical home" to ensure continuity of care, increased availability of patient navigators, and more female and minority health care providers. The report also called for improved insurance coverage, linguistically accessible information services, and optimized HPV testing and vaccine development.

The CRN reported in 2005 that more than half of cervical cancer cases among 833 women in seven Health Maintenance Organization managed care plans were attributable to lack of Pap testing. Women older than 39 and women living in a high-poverty area or with low educational levels were more likely to have not received a Pap test. Research to improve the use and effectiveness of cervical cancer screening includes a recent clinical trial* which compared a single-visit approach to cervical cancer screening and treatment versus the standard of care – Pap testing and referral for a follow-up visit – in an underserved population. Women in the single-visit group were significantly more likely to receive definitive treatment within 6 months of diagnosis of high-grade lesions

NCI's CIS, in partnership with the Center for Disease Control and Prevention (CDC), ACS, and the United States Department of Agriculture, is conducting a pilot project called "TEAM-UP: Cancer Screening Saves Lives." This project is using evidence-based interventions to increase participation in cervical and breast cancer screening programs among never and/or rarely screened women in eight states with persistently high cervical and breast cancer incidence and mortality rates.

In cooperation with CRCHD and the Deep South Network for Cancer Control, NCI researchers are conducting a study of cervical cancer screening in the Mississippi Delta using self-collected cervical specimens tested by sensitive HPV DNA assays. The study will determine whether self-testing for HPV can be used to screen women reluctant or unable to obtain Pap tests. The NCI CRCHD is also administering development of an innovative Patient Navigator Research Program (http://crchd.cancer.gov/pnp/pnrp-index.html), focusing on four cancers for which screening tests are available: breast, cervical, prostate and colorectal. (See Cancer Control, Survivorship, and Outcomes research in the Breast Cancer section of this report.)

Race-Related HPV Variants. Researchers* found that, in a population of women positive for HPV16 and HPV18, White women and Black women tended to have different genetic variants of these viruses, termed European and African variants respectively. Investigators suggest the need for research to examine possible mechanisms of variant-specific immune evasion and potential therapeutic implications.

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OVARIAN CANCER

In 2007, approximately 22,430 women in the United States are expected to be diagnosed with ovarian cancer, and approximately 15,280 are expected to die of the disease. Incidence rates decreased by 0.7 percent per year between 1985 and 2003. 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 93 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 69 percent for regionally advanced stages and 30 percent for stages with distant metastases.

Ovarian Cancer SPOREs. NCI's five Ovarian Cancer SPOREs (http://spores.nci.nih.gov/current/ovarian/ovarian.html) frequently collaborate to develop prognostic, screening, prevention, and therapeutic tools for ovarian cancer. SPORE activities include identification of an optimally sensitive panel of known markers, such as CA-125, and novel markers for the early detection of ovarian cancer in conjunction with transvaginal ultrasound. Examples of other activities include clinical trials of targeted therapy with vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) blockers in combination with chemotherapy, gene therapy in combination with chemotherapy, and development of therapies that target the phosphatidylinositol 3 kinase (PI3K) pathway, which is frequently mutated in ovarian cancer. Another project aims to develop strategies to identify ovarian cancer patients least likely to respond to modern platinum/taxane-based treatments and to develop therapeutic strategies to attack cancer cells in these patients.

BIOLOGY

The Cancer Genome Atlas (TCGA). The pilot of the NCI and National Human Genome Research Institute's (NHGRI) TCGA will assess the feasibility of developing a useful atlas of the changes in the human genetic blueprint associated with all types of cancer, beginning with ovarian, lung, and brain cancers.

Molecular Classification. A study using DNA microarray technology helped to clarify the relationship between low malignant potential (LMP), low-grade, and high-grade serous ovarian tumors. The study suggests that LMP tumors are not early precursors of aggressive ovarian cancer, as had been suspected, but may be part of an entirely different class of tumors. Researchers also showed that low-grade serous tumors are more similar to LMP tumors than to high-grade serous tumors. This finding suggests that women with low-grade tumors may benefit from different therapies than those given to patients with high grade tumors.

Mouse Models. Several new mouse models are useful for elucidating the biology of ovarian cancer to inform development of potential ovarian cancer treatment strategies. For example, NCI-MMHCC researchers found elevated levels of the protein COX1 in three mouse models (each involving changes to different genes) of human epithelial ovarian cancer (EOC). However, the related COX-2, which is associated with a variety of cancers, was not elevated. Specific inhibition of COX-1 led to significant tumor reduction in all three models. NCI-MMHCC has also developed mouse models for endometroid ovarian cancer, a subtype of EOC. Another model was designed to permit molecular characterization of BRCA1-associated EOC.

In another study, researchers identified and characterized a distinct sub-population of ovarian cancer stem-like cells in a genetically engineered mouse cell line. Researchers are using the mouse cells to study the role of stem-like cells in recurrent ovarian cancer and to design new targeted therapeutic agents. They have shown that these putative tumor stem cells are sensitive to a glycoprotein called Mullerian Inhibiting Substance (MIS), and that MIS is able to enhance subclinical doses of standard chemotherapy for EOC and inhibit growth of both human and mouse EOC cell lines.

Mouse models are also used to inform potential strategies for cancer detection. Optical imaging of mouse models is helping researchers to locate microscopic intraperitoneal metastases, which commonly recur after surgery because small tumor foci escape detection within the complex anatomy of the peritoneal cavity and mesentery. Researchers are working towards bringing this technology into the clinic.

An association between chronic behavioral stress and increased tumor burden and more invasive growth of ovarian carcinoma cells was identified using yet another mouse model. The effects of stress seemed to be mediated by angiogenic processes, providing clues for the development of cancer treatment strategies.

RISK FACTORS

In the United States approximately 1 woman in 70, or 1.4 percent, will develop ovarian cancer during her lifetime. Researchers are investigating potential mechanisms by which reproductive, demographic, and lifestyle factors affect risk of ovarian cancer. Oral contraceptive use, having had at least one full term pregnancy, and having breast fed are associated with a reduced risk of ovarian cancer. Tubal ligation and hysterectomy may be associated with a decreased incidence of ovarian malignancy. HRT use in postmenopausal women may be associated with an increased risk of developing ovarian cancer. However, the single greatest risk factor is a family history of the disease. 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 inherited mutations in the *BRCA1* or *BRCA2* genes cause 5-10 percent of ovarian cancers.

Hormones. Researchers who evaluated self-reported data from a large cohort study found that women aged 50-71 who took unopposed estrogen for 10 or more years had a significantly increased risk of ovarian cancer, whereas women who took unopposed estrogen for a shorter period had no increased risk. Also, women with intact uteri who took estrogen plus progestin were about twice as likely to develop ovarian cancer as women with intact uteri who never used hormone therapy.

Cancer Family Registries. The Cancer Family Registries (http://epi.grants.cancer.gov/CFR/) is an international registry system available to researchers who are planning to conduct population- and clinic-based interdisciplinary research with a main focus on the genetic and molecular epidemiology of breast, ovarian, and colorectal cancers.

PREVENTION

Prophylactic Surgery. Women who are at high risk of ovarian cancer because they carry mutated *BRCA1* and *BRCA2* genes can reduce by about 60 percent their risk of developing this and other cancers of the reproductive organs by having preventive surgery to remove their ovaries and fallopian tubes, according to the largest prospective study yet done on this issue. NCI has completed enrollment of 2,300 women to a multi-center clinical trial that will further quantify the extent of breast and ovarian cancer risk reduction after preventive removal of the ovaries and fallopian tubes in women at high risk for ovarian cancer. The study will also assess quality of life and incidence of non-cancer diseases related to premature menopause. Researchers will evaluate a novel approach to ovarian cancer screening based on quantitative assessment of changes in the tumor marker, CA-125, over time. Study investigators are developing and validating a model of medical decision-making related to the choice of surgery vs. screening.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Proteomics. Researchers conducting a national, multi-center clinical trial will collect blood samples from patients after successful treatment of advanced ovarian cancer. These samples will be used to develop proteomic technology to detect recurrent ovarian cancer well before symptoms appear. The long-term goal of this project is to develop a means of detecting early-stage ovarian cancer.

Another experimental blood test may one day help diagnose ovarian cancer and mesothelioma. The test measures levels of mesothelin, a protein shed into the blood of patients with these cancers. Analyses showed that mesothelin levels were elevated above control levels in 14 out of 21 patients with ovarian cancer and 40 out of 56 patients with mesothelioma. Other observations suggest that this blood test may be useful for monitoring disease progression. Further research is needed to validate these initial findings.

National Ovarian Cancer Early Detection Program: Screening and Genetic Study. This multi-site clinical trial seeks to identify effective screening and genetic testing methods to identify women at increased risk for developing ovarian cancer; identify and develop highly sensitive and specific early detection tumor markers; develop therapies based on molecular, genetic, and biochemical insights; and determine the utility of minimally invasive office diagnostic laparoscopy and the "Ovarian Pap Test." http://www.clinicaltrials.gov/ct/gui/show/NCT00005095

Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) Trial. Preliminary results from the ovarian cancers screening component of the PLCO trial were released in November 2005. Screening with transvaginal ultrasound and a blood test for the tumor marker CA-125 did find tumors, but also yielded many false positives. Based on these results, the investigators concluded that these tests cannot currently be recommended for widespread screening in the general population. Several studies are using blood samples collected from asymptomatic PLCO participants who later developed ovarian cancer. These studies are researching biomarkers that could be developed into diagnostic tests for detection of early stage ovarian cancer. PLCO has also provided DNA samples from thousands of patients and healthy controls for whole genome scanning to identify breast cancer susceptibility genes and provide a better understand the biological basis of breast cancer.

TREATMENT

The treatment of ovarian cancer is evolving rapidly as results emerge from ongoing clinical trials. Standard post-surgery chemotherapy for newly diagnosed ovarian cancer usually consists of treatment with a platinum-based drug (e.g. carboplatin or cisplatin) in combination with either alkylating agents or paclitaxel. Patients whose disease recurs more than six months after completion of chemotherapy are usually re-treated with a platinum-based drug.

Intraperitoneal Chemotherapy. In January 2006, NCI issued a rare clinical announcement to raise awareness about intraperitoneal (IP) chemotherapy (delivered by a catheter to the abdominal cavity) for ovarian cancer. The announcement followed striking clinical trial findings that women with ovarian cancer who received intravenous (IV) and IP chemotherapy after removal of most tumor tissue lived on average 16 months longer than women who had surgery and IV chemotherapy alone. Before this announcement, IP chemotherapy was widely regarded as old technology and only given to about 1 percent of women with ovarian cancer, in part because of increased toxicity associated with the delivery method. However, even though patients in the IP/IV group experienced more complications, most problems were manageable and transient. Both groups reported a similar quality of life one year after treatment.

New Drug Strategies. NCI-supported investigators are exploring the effectiveness of various drug combinations and treatment regimens for treating advanced stage and recurrent ovarian cancer. Drugs currently in clinical testing include Velcade, docetaxel (Taxotere®), erlotinib (Tarceva®), gemcitabine (Gemzar®), ixabepilone (BMS-247550), liposomal doxorubicin, nitrocamptothecin, oxaliplatin (Eloxatin®), sorafenib (BAY 43-9006), Avastin, TLK286, and topotecan. In 2006, clinical trial researchers reported that patients with recurrent ovarian cancer treated with a combination of gemcitabine plus carboplatin lived a median of 2.8 months longer than those who received carboplatin alone. Both groups of women experienced about the same quality of life. Other innovative approaches to the treatment of advanced ovarian cancer in development or in early trials include therapeutic vaccines, monoclonal antibody therapies, donor lymphocyte infusion, nonmyeloablative allogeneic transplantation, gene therapy, and antiangiogenic agents.

Preclinical Research. In a mouse model for mesothelin-bearing tumors, the combined administration of paclitaxel and the immunotoxin-SS1P was much more effective than either treatment alone, and caused long-lasting complete remission in the mice. SS1P targets the protein mesothelin which is present in 70 percent of ovarian cancers. Paclitaxel is known to be effective against ovarian cancer and prior research has shown some treatment effect of SS1P alone in a phase I trial that included patients with ovarian cancer. The investigators hypothesize that the synergistic effects of paclitaxel and SS1P will work better than either agent alone.

Surgery. According to a May 2005 report*, removing the aortic and pelvic lymph nodes during surgery for advanced ovarian cancer does not improve overall survival. On average, women receiving lymphadenectomy surgery had a 7 month longer disease-free survival, but also experienced more complications associated with the surgery.

CANCER CONTROL, SURVIVORSHIP, AND OUTCOMES RESEARCH

Communication. In 2006, NCI updated the *What You Need to Know about Ovarian Cancer* booklet, (available at www.cancer.gov/publications), which answers patients questions about symptoms, diagnosis, staging, and treatment.

Fertility Issues. The American Society of Clinical Oncology (ASCO) has released guidelines for addressing fertility preservation options with patients prior to cancer treatment. The ASCO-convened expert panel noted that many oncologists either do not discuss the possibility of treatment-related infertility or do so only suboptimally. The panel also found that fertility preservation is of great importance to many patients and properly addressing the issue was a positive factor in patients coping emotionally with cancer. The NCI supports research on this topic and in 2005, provided funds to researchers at M.D. Anderson Cancer Center for a scientific workshop, Parenthood After Cancer: Today's Options, Tomorrow's Hopes.

Outcomes. Researchers analyzing SEER data on women aged 65 and older with ovarian cancer found that women treated by a gynecologic oncologist had marginally better survival rates than those treated by general oncologists and markedly better outcomes compared with patients treated by general surgeons. A companion study found that specialized training, more than surgeon volume (the number of relevant surgeries performed by the surgeon), improved patient outcomes.

* Research studies denoted with an asterisk may not have received NCI funding. However, these advances were included because they are significant contributions to research on cancers in women.

ENDOMETRIAL CANCER

Cancer of the corpus uteri, or endometrium, is the fourth most common invasive cancer among women in the United States. An estimated 39,080 American women will be diagnosed with uterine cancer in 2007, and approximately 7,400 will die from the disease. The incidence of endometrial cancer declined from 1975 to 1988, increased slightly over the next decade, and again has begun to decline. Average incidence rates for White women were 24.5 per 100,000 from 1999 to 2003, while incidence rates for Black women were much less at 19.7 per 100,000. Average mortality rates show an opposite pattern, with the death rate for White women at 3.9 per 100,000 and death rates for Black women nearly double that at 7.1 per 100,000.

Gynecologic Cancer SPORE. The Gynecological Cancer SPORE at The University of Texas M.D. Anderson Cancer Center conducts innovative translational research for the prevention and treatment of uterine tumors. Major projects of the SPORE aim to:

- Decipher the fundamental molecular differences between Type 1 and Type 2 endometrial cancers.
- Provide a panel of molecular markers that will be useful in endometrial cancer prognosis and in identifying patients at risk for developing the malignancy.
- Dissect the molecular pathways involved in estrogen and progesterone mediated growth regulation of the uterine endometrium and smooth muscle.
- Promote novel strategies in the chemoprevention of endometrial cancer.
- Understand, at the molecular level, the complex mechanism of action of SERMs such as tamoxifen, raloxifene, and a new third generation SERM, Arzoxifene, in the epithelial and smooth muscle compartments of the uterus.

BIOLOGY

Mouse Models. Researchers are developing mouse models in order to study molecular genetic abnormalities which may be predictive of progression of precursor lesions. Because of the present inability to predict which precursor lesions may progress and the morphologic ambiguities of distinguishing between complex atypical hyperplasia (CAH) and uterine endometrioid carcinoma (UEC), numerous women undergo hysterectomy for benign, non-invasive disease. A more thorough understanding of the differences between CAH and UEC, and the role of both hormonal and genetic factors on the development and progression of endometrial tumorigenesis would substantially improve the diagnosis and management of women with endometrial lesions.

Specimen Resources. The Gynecologic Oncology Group tissue bank provides specimens for researchers studying endometrial cancer. Requests for tissues are assessed by peer review. The Tissue Expediter and the Specimen Resource Locater Web site (http://pluto3.nci.nih.gov/tissue/default.cfm) can assist researchers to identify sources of tissue.

RISK FACTORS

Scientists have found significant increases in endometrial cancer risk for women who used estrogen and progesterone, including women who used continuous estrogen plus progestin regimens. Elevations in risk persisted at least 10 years after last use. These results suggest the need for continued monitoring of long-term effects of unopposed estrogen and estrogen plus progestin menopausal hormone therapies. Other factors associated with increased risk for endometrial cancer include personal history of breast cancer, tamoxifen use, obesity, age, lack of physical activity, hereditary nonpolyposis colon cancer (HNPCC, or Lynch Syndrome), and diabetes and other medical conditions, but possible mechanisms remain obscure. Cigarette smoking and high intake of complex carbohydrates appear to reduce risk. Recent research suggests that family history of breast cancer may not be associated with increased risk for endometrial cancer. Tamoxifen, used in the prevention and treatment of ER-

positive breast cancer, has also been linked with an increased risk of endometrial cancer. Studies indicate that tamoxifen may have delayed effects, such as the increased risk of rare but aggressive uterine tumors of unclear pathogenesis. New drugs, such as AIs, that can be used alone or in combination with tamoxifen for treatment of hormone-dependent tumors are being investigated.

PREVENTION

NCI prevention studies focus on developing breast cancer prevention and treatment agents that do not increase endometrial cancer risk; developing chemoprevention methods for endometrial cancer; and determining the effects of obesity and nutrition on endometrial cancer. A Phase II randomized study examining the role of progestins (medroxyprogesterone) versus low dose ethinyl estradiol and norgestrel for the prevention of endometrial cancer in HNPCC patients is ongoing.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Researchers are studying the *PTEN* tumor suppressor gene to establish whether it has clinical cancer predicative value for endometrial cancer. *PTEN* is altered very early in endometrial carcinogenesis and displays decreased protein expression in 75 percent of premalignant and malignant endometrioid lesions. The goal is to develop a strategy for early detection and chemoprevention of endometrial cancer.

TREATMENT

Surgery. Surgery, including hysterectomy and bilateral salpingo-oophorectomy, is the most common treatment for endometrial cancer. Researchers are identifying adjuvant chemotherapy regimens that can improve survival in women with endometrial cancer. In women who have not completed childbearing, alternative treatments that address fertility issues are being investigated. In November 2006, NCI joined with the United Kingdom Cancer Research Institute and Medical Research council to co-sponsor a state-of-the-science meeting for treatment issues in endometrial cancer. Investigators from clinical trials groups around the world identified 14 key trials on which they hope to collaborate.

Chemotherapy. The NCI-funded Gynecologic Oncology Group (GOG; http://www.gog.org/) conducts research focused on women with pelvic malignancies, including endometrial cancer. In a phase III GOG clinical trial, post-surgical adjuvant chemotherapy with cisplatin and doxorubicin improved survival by 33 percent in women with advanced endometrial cancer, compared to women who were treated with standard whole abdominal radiation treatment. Because toxicity can be a problem with this chemotherapy regimen, GOG is conducting a phase III trial investigating the better tolerated carboplatin and paclitaxel therapy.

Radiation Therapy. Results of a retrospective analysis using SEER data from more than 21,000 women with early-stage endometrial cancer demonstrate a significant survival benefit with adjuvant radiation therapy (RT) in subsets of women with high-risk disease. Overall and relative survival were improved in women with grade 1, 3, and 4 tumors that had spread into the layer of muscle around the uterus (stage IC). Further investigation is needed to determine which patients with early-stage disease are at highest risk for recurrence after surgery and how best to treat them.

Hormonal Therapies. NCI is conducting a phase II pilot study to compare the efficacy of medroxyprogesterone in patients with progesterone receptor-positive versus progesterone-receptor negative endometrial adenocarcinoma of the uterine corpus.

Combined Modality and Targeted Therapies. NCI supports studies comparing different chemotherapies, alone or in combination, and with or without radiotherapy. Most trials are in Phase I or II. Studies are also in progress to test the effectiveness of the molecularly targeted agents, Herceptin, Avastin, sorafenib, temsirolimus (CCI-779),

and the drug 852A for treating endometrial cancer. Side effects of therapy and quality-control issues in radiation equipment are also being investigated.

HEALTH DISPARITIES

Previous studies have suggested that the disparities in survival for Black women compared with White women with endometrial cancer were due to differences in treatment. However, a recent retrospective analysis of data from four GOG randomized treatment trials found that in a setting where all patients received equal care, Black women had a 25 percent greater chance of dying than White women with the same diagnosis. A second study found differences in tumor gene expression patterns between Black and White women with advanced stage endometrial cancer. These studies suggest that, while treatment disparities should still be investigated, socioeconomic, biologic, and cultural factors should also be addressed to decipher the causes of this health disparity.

LUNG AND OTHER TOBACCO-RELATED CANCERS

Tobacco use is the leading preventable cause of premature death in the United States. Each year, more than 440,000 Americans die of tobacco-related disease, accounting for 1 in every 5 deaths. Cigarette smoking is responsible for more than 30% of cancer deaths annually in the United States. Research shows that tobacco use causes an increasing number of cancers of particular concern to women, including lung, cervical, and ovarian cancers. Scientific evidence also suggests a causal relationship between smoking and colorectal cancer. Epidemiological studies exploring a possible link between smoking and breast cancer have yielded inconclusive results, although animal, human biomarker, and *in vitro* cellular studies strongly suggest that tobacco carcinogens may be involved in breast cancer development. Tobacco use is also a causal factor in leukemia and cancers of the bladder, esophagus, kidney, larynx, oral cavity, pancreas, and stomach. Since 1987, more women have died each year of lung cancer than of breast cancer, which had been the major cause of cancer death in women for more than 40 years. It is estimated that 98,620 women will be diagnosed with lung cancer in 2007 and 70,880 women will die from this disease in the United States. Although incidence and death rates in men have been declining since the early 1980s and 1990s, respectively, these rates for women continued to increase. The latest analysis of SEER data now shows an attenuated increase in mortality rates from 1991 to 2003. A recent analysis suggests that the discrepancy in declining incidence rates between men and women largely reflects smoking prevalence from past decades. High death rates reflect our limited ability to detect lung cancer at an early and potentially more curable stage. Over half of new cases are diagnosed in advanced stages of the disease, for which the 5-year relative survival is only 2.1 percent. Black men have the highest death rates from lung cancer followed by somewhat lower rates for non-Hispanic White men. The highest lung cancer death rates occur in non-Hispanic White women with slightly lower rates found in Black women.

Women, Tobacco, and Cancer. The Women, Tobacco, and Cancer Working Group, a public/private partnership led by NCI, released the report, *Women, Tobacco, and Cancer: An Agenda for the 21st Century*, in July 2004 (http://searchosp1.nci.nih.gov/whealth/reports/wtobacco.pdf). The report recommends strategies to meet five overall goals in the areas of discovery, development, delivery, partnerships, and evaluation and surveillance that will contribute to reducing and ultimately eliminating the harmful health effects of smoking in women. The report has been disseminated to the global tobacco research and advocacy communities. In response, the Tobacco Research Network on Disparities (TReND) initiated the Low SES (socioeconomic status) Women & Girls Project in 2004 to strategically address and examine the effects of multiple tobacco control policies on diverse populations of low SES women and girls. A scientific meeting, *Tobacco Control Policies: Do They Make a Difference for Low SES Women and Girls?* was convened in September 2005. The project aims to stimulate new research, review existing research, and, as a result of its findings, inform the development and implementation of policies and programs by practitioners that may reduce tobacco use among this population.

Lung Cancer Program (LCP). The NCI Lung Cancer Integration and Implementation (I2) team led to the establishment of the LCP. The central focus of this program will be to support research on lung cancer biology, early detection, and treatment. The LCP will also provide resources to CISNET to improve the understanding of the impact of cancer control interventions in tobacco cessation, early detection and screening, and therapy. The LCP will also support tissue acquisition, processing and archiving in the National Lung Screening Trial.

Transdisciplinary Tobacco Use Research Centers (TTURCs). TTURCs (http://dccps.nci.nih.gov/tcrb/tturc) help provide the needed infrastructure to facilitate a transdisciplinary approach to the full spectrum of basic and applied research on tobacco use to reduce the disease burden of tobacco. A group of seven TTURCs is funded by NCI, the National Institute on Drug Abuse, and the National Institute on Alcohol Abuse and Alcoholism. TTURC researchers study a range of topics including, the etiology of tobacco use and addiction, the impact of advertising

and marketing, prevention of tobacco use, treatment of tobacco use and addiction, identification of biomarkers of tobacco exposure, and identification of genes related to addiction and susceptibility to harm from tobacco.

Lung Cancer SPOREs. NCI currently funds seven lung cancer SPOREs (http://spores.nci.nih.gov/current/lung/lung.html). The Lung SPORE at the University of Pittsburgh Cancer Institute has a focus on improving detection and treatment of lung cancer and understanding the mechanisms of women's susceptibility to this disease. Researchers at this SPORE are investigating the role of estrogen receptors in lung cancer in women. A clinical trial is planned to explore possible protective effects of administering ER antagonists to lung cancer patients.

BIOLOGY

Gender Differences. Among those who smoke, women are more likely than men to get more aggressive forms of lung cancers. Also, among people who have never smoked, women are more than twice as likely than men to develop lung cancer. These patterns suggest biological differences in the way lung cancer develops in men and women. A Southwest Oncology Group (SWOG) study will investigate why women seem to get a different type of lung cancer than men, and at an earlier age, especially if they have never smoked. The study will also seek to better understand the factors that cause lung cancer in both men and women who do not smoke.

The Cancer Genome Atlas (TCGA). The pilot of the NCI and NHGRI's TCGA will assess the feasibility of developing a useful atlas of the changes in the human genetic blueprint associated with all types of cancer, beginning with lung, brain, and ovarian cancers.

RISK FACTORS

Tobacco Use. A multicenter case-control study of lung cancer and tobacco use is ongoing in Milan, Italy. This trial includes collection of extensive questionnaire and biospecimen data and is unique in collecting information on many other factors, including tumor tissue obtained in surgery, demographics, tobacco use, alcohol use, occupational exposures, diet, and medical illness. Investigators are now evaluating differences in expression arrays in lung adenocarcinomas, normal lung tissue, and matched lymphocytes among never smokers, previous smokers, and current smokers.

The PLCO (http://www.cancer.gov/prevention/plco/) and the Shanghai Women's Health Study (http://epi.grants.cancer.gov/ResPort/ShanghaiWomen.html) are large, ongoing cohort studies that include biospecimens and questionnaire data with a focus on tobacco-related cancers. Information from these cohorts can be used in a variety of studies related to the effects of tobacco exposures.

NCI also supports transdisciplinary research on the interplay of behavior, chemistry, toxicology, biology, and epidemiology to determine the cancer risk potential of reduced-exposure tobacco products. Current scientific evidence is insufficient to evaluate whether these new products actually reduce the user's exposure or risk for tobacco-related diseases.

Second Hand Smoke. Two recent studies emphasized the health risks of exposure to second hand smoke. One study showed that patients who had been exposed to high levels of second hand tobacco smoke over many years did not live as long on average as patients who had been exposed to lower levels. A European study* found an association between exposure to second hand smoke and risk of lung cancer. The risk was higher among former smokers than among never smokers. Furthermore, infants who were exposed to second hand smoke were up to three times more likely to develop lung cancer as adults.

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Diet. A large chemoprevention study has shown that a high intake of phytoestrogen compounds decreases the risk of lung cancer. Investigators reported that study participants who ate the most phytoestrogens reduced their lung cancer risk by 46 percent compared with those who ate the lowest amount. However, women benefited less than men, and former smokers benefited less than never smokers. The investigators cautioned that much more research is needed to prove a definitive chemoprevention effect.

Genetics. Studies by NCI and others have confirmed that genetic mutations associated with non-small-cell lung cancer (NSCLC) occur preferentially in certain subsets of patients, including women, patients who have never smoked, patients with adenocarcinoma, and patients of Asian descent. Two recent studies have found epidemiologic evidence of familial risk for lung cancer. Both studies found that the incidence of lung cancer was higher in family members of patients with this disease compared with family members of healthy individuals, even after eliminating the effects of smoking on risk. One study also found that family members of Black patients with early-onset lung cancer are twice as likely to develop lung cancer, compared with family members of White patients with this disease. Further research is needed to identify the genetic factors contributing to lung cancer risk suggested by these findings.

Proteomics. Scientists are elucidating the role of proteins in the development of tobacco-related cancers to identify strategies to prevent and treat this disease. Recent studies show that activation of the protein AKT occurs early in the development of tobacco-related cancers, such as lung cancer. This critical protein may form the basis of a decision-making tool to individualize care for patients with early-stage NSCLC. Another study has shown that long-term smoking cessation increases the blood levels of an important anti-inflammatory protein, CC10, that may play a role in combating the development of lung cancer. While this study suggests that quitting smoking may lead to repair of some lung damage, further studies are needed to elucidate CC10's role in lung cancer.

PREVENTION AND CONTROL

Tobacco Use and Addiction. A study funded in part by NCI found that children aged 10 to 17 smoked less and displayed more favorable antismoking attitudes and beliefs when they had been recently exposed to antismoking TV advertisements sponsored by state public health departments. The results show that state-sponsored advertising, while much less frequent than "anti-tobacco" advertising sponsored by the tobacco industry, is much more effective. Another study found that adolescents age 10 to 14 who watched the most smoking in the movies were almost three times more likely to start smoking than their peers who watched the least amount of smoking in movies. This result was found in all regions of the country, regardless of race and ethnic group.

Tobacco Cessation. The importance of smoking cessation was emphasized by the recent findings of the National Heart, Lung, and Blood Institute (NHLBI) Lung Health Study, the first ever report to demonstrate that smoking cessation results in lower lung cancer mortality. However, results from the annual National Health Interview Survey (NHIS) show that the steady decline seen in smoking rates over the last 8 years had come to a halt. The authors cited smaller annual increases in the price of cigarettes, increased tobacco industry expenditures on price discounts, and a significant drop in state tobacco control program funding as possible contributors to their findings. Furthermore, NCI's HINTS has revealed that smokers underestimate their relative risk of lung cancer compared with nonsmokers. In addition, HINTS reveals that many current and former smokers incorrectly agree with several myths about smoking and health, with more than half agreeing that exercise undoes most of tobacco's negative effects.

Tobacco Control Interventions. NCI supports a variety of culturally-appropriate interventions to encourage and help tobacco users to quit. The NCI and CDC "Quit Now" Challenge of October 2006 featured inspirational stories of people who want to quit smoking. Tobacco users submitted stories in their own words about why they wanted to "Quit Now." In February 2006 stories were chosen from successful quitters, who were given public opportunities to share their experiences to help others quit. In November 2005, ABC-TV partnered with NCI, CDC, and the North

American Quitline Consortium to air "Quit to Live: Fighting Lung Cancer," a televised series of reports on smoking cessation and lung cancer prevention.

Smoking-related NCI publications available to the public include *Clearing the Air,* a manual designed to help smokers quit; *Clear Horizons,* a quitting guide for those older than 50; the Spanish-language guide on smoking cessation, *Guia para Dejar de Fumar; Pathways to Freedom*, for African American smokers; and *Fact Sheets and FAQ,* for smokers and non-smokers looking to learn about the impact of smoking (http://www.smokefree.gov/info.html).

NCI also provides resources to inform the development of effective tobacco control programs. NCI and CDC partnered with the Robert Wood Johnson Foundation to launch the "Helping Young Smokers Quit," initiative. This two-phase project has gathered information on a representative sample of youth smoking-cessation programs throughout the U.S. and will evaluate whether these programs have helped youth quit smoking. The monograph, *ASSIST: Shaping the Future of Tobacco Control* (http://dccps.cancer.gov/tcrb/monographs/16/index.html), released in June 2005, documents models and lessons learned and describes case studies from the 8 year American Stop Smoking Intervention Study for Cancer Prevention (ASSIST) demonstration project. The monograph provides concrete examples for building long-term capacity and positive behavioral health changes by applying these policy and media approaches. The monograph *Evaluating ASSIST – A Blueprint for Understanding state-Level Tobacco Control* was released in 2006. Through the International Tobacco and Health Research and Capacity Building program, NCI and partners support transdisciplinary research and capacity building projects that address the burden of tobacco consumption in low- and/or middle-income nations.

Effectiveness of Interventions. Researchers released a 13-year follow-up study of NCI's Community Intervention Trial for Smoking Cessation (COMMIT). Researchers found that the higher quit rates in COMMIT intervention communities (versus comparison communities) achieved while the study was funded, were absent 8 years after the program ended. This suggests that continued impact of tobacco control interventions require sustained funding. The study also found that quit rates were highest in states with both strong tobacco-control policies and aggressive tobacco control programs.

Cessation Treatments. Many studies have suggested that women may have greater difficulty quitting smoking than men. A TTURC study examined gender differences in smoking cessation in a placebo-controlled trial of bupropion with behavioral counseling. They found that bupropion particularly benefited men who smoked more than one pack of cigarettes per day at baseline, and conversely, women who smoked a pack or less. These findings suggest that bupropion treatment may help reduce the gender disparity in prolonged abstinence rates among lighter smokers.

Chemoprevention. NCI supports preclinical studies focused on identifying and prioritizing agents that prevent cancers in tobacco-susceptible organ systems. Clinical researchers are evaluating the efficacy of chemopreventive agents in specific cohorts of former smokers.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Imaging. Researchers have completed enrollment of 50,000 current smokers and former smokers into the ACRIN and NCI-supported National Lung Screening Trial (NLST; http://www.nci.nih.gov/nlst). Approximately half of the participants are women and about 4 percent are racial/ethnic minorities. This 8-year, multi-site study will determine whether lung cancer screening using low-dose spiral computed tomography in high-risk populations reduces mortality from this disease compared with standard x-ray screening. NLST scientists will also assess the stage of tumors when first detected, quality-of-life and psychological issues for people who test positive for lung cancer, economic consequences, and other potential differences between the two screening methods.

Preliminary results from the PLCO Cancer Screening Trial, reported in 2006, show that chest x-rays can detect lung cancer earlier, but also produce many false-positives that cause needless extra tests. Further analysis will reveal if the group receiving screening x-rays has a lower lung cancer mortality rate than the group receiving usual care.

The recently created NCI Imaging Archive (NCIA) contains large collections of lung CT and PET scans as a research resource for software developers. This resource will enable development of algorithms for computer-aided detection and diagnosis of small lung nodules. NCI, with the NIH Biomarker Consortium, is also supporting a clinical trial to evaluate PET as a biomarker for prognostic measurement of treatment-related tumor volume changes in patients with NSCLC.

Molecular Signatures. Researchers are developing tests that may one day be used for clinical detection, diagnosis, and treatment planning. For example, the experimental "metagene" model may help predict the risk of recurrence for patients with early stage lung cancer and determine which patients would most likely benefit from adjuvant chemotherapy. A prospective study is needed to assess the model after two evaluation studies showed an overall predictive accuracy for recurrence risk of 72 percent and 79 percent. The metagene model is similar to the genomic strategy used in the TAILORx breast treatment trial. Other research suggests that testing the sputum of individuals at high risk for lung cancer to detect genes silenced by methylation is a promising screening strategy for early signs of the disease. Another promising approach to lung cancer screening involves gene profiling of cells obtained from the airway during fiberoptic bronchoscopies.

Early research is identifying other molecular signatures that may one day prove useful for detection, diagnosis, or prognosis of lung cancer. For example, investigators have found that the increased expression patterns of certain microRNAs (miRNAs) may be associated with poorer patient prognosis, suggesting the need for more aggressive treatment. Researchers from the International Adjuvant Lung Cancer Trial* (IALT) identified lack of expression of the DNA-repair protein ERCC1 as a possible predictor of increased survival after cisplatin-based adjuvant chemotherapy. Further studies are needed to determine whether prospective testing for ERCC1 expression will predict patient response to therapy.

TREATMENT

Chemotherapy. NCI supports clinical trials to improve outcomes and reduce treatment toxicity in patients with lung cancer by testing regimens of drug combinations for adjuvant chemotherapy. One study showed that adjuvant chemotherapy with cisplatin-based regimens prolongs survival in patients with resected stage II-III disease.

Nicotine Effects Investigators treating NSCLC cell lines with several chemotherapy drugs found that nicotine suppressed the cell killing ability of each drug. The investigators stress the need to take the effects of nicotine into account when developing new treatments for lung cancer.

Molecularly Targeted Therapy. Two EGFR inhibitors, gefitinib (Iressa®) and Tarceva® are used for treatment of some NSCLC patients. These drugs act by inhibiting the angiogenesis needed for tumor growth. Because two trials did not show that Iressa improved survival of patients with lung cancer, the FDA restricted use of this drug in 2005 to patients who are currently taking it or have previously benefited from it. Since only about 10 percent of advanced-stage NSCLC patients respond well to EGFR inhibitors, NCI supports research to define genomic and proteomic markers for prediction of patient response to these agents. Researchers are also identifying strategies to combat acquired resistance to EGFR inhibitors in patients receiving long term treatment with the drugs.

In 2006, Avastin was approved by the FDA for use in advanced NSCLC patients in combination with paclitaxel and carboplatin after clinical results showed that this treatment regimen improved survival. However, a preliminary

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analysis in a separate study suggests that female patients with lung cancer may not respond as well as male patients to Avastin. NCI supports clinical trials of other molecularly targeted agents, including sorafenib and cetuximab (Erbitux®).

Preclinical research is yielding information about potential new targets for lung cancer therapy. Promising strategies include inhibition of the AKT protein pathway with phosphatidylinositol ether lipid analogs (PIAs) and inhibition of the protein ErbB3, which appears to interact with AKT to maintain proliferation and invasiveness of lung adenocarcinoma.

Age-Related Factors. Prior studies have shown that chemotherapy for older patients with NSCLC is associated with some survival benefits, but also with significant toxicity. However, a phase II study has shown promising results for the drug erlotnib, as well as tolerable toxicity, as a first line treatment for elderly patients with advanced NSCLC. Another study* showed that adjuvant platinum-based chemotherapy for elderly patients with NSCLC improves survival, without an increase in treatment-related toxicity or hospitalization compared to younger patients.

HEALTH DISPARITIES

TReND, supported by NCI and the American Legacy Foundation, conducts interdisciplinary research to understand tobacco-related health disparities, translate scientific knowledge into practice, and inform public policy. This is the only national research network on tobacco and health disparities and offers a unique forum for stimulating scientific inquiry, promoting scientific collaborations, and evaluating the scientific evidence of research.

SES. The 2007 report of the NHIS reported that smoking prevalence among Americans with graduate degrees fell to 7.1 percent, while prevalence among those with a graduate equivalency degree (GED) was 43.2 percent. Prevalence was also higher among people living below the poverty level than among those at or above the poverty level (29.9 percent vs. 20.6 percent). NCI-supported studies are looking at the influence of SES on various aspects of tobacco use and cessation. One of the first major questions addressed by TReND is focused on the effects of tobacco control policy and women of low SES.

Race and Ethnicity. A large prospective study has found that both Blacks and Native Hawaiians had significantly greater risks of lung cancer related to smoking compared with Whites, Hispanics, and Japanese Americans. These racial and ethnic differences were greatest among those who smoked 10 cigarettes or less a day. For smoking rates as high as 30 cigarettes a day, the difference in risk among groups was minimal.

A retrospective study* of 97 Black patients and 184 White patients with early stage lung cancer found that Black patients were far more likely than White patients to decline offered surgical therapy. However, the chances of 5-year survival are as high as 50 percent in patients with early stage disease who are treated with surgery, whereas median survival is less than 1 year for those who decline surgery. This and other studies suggest that factors contributing to this disparity may include a lack of trust in the health care system and a belief that surgery to treat lung cancer can actually cause the disease to metastasize.

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COLORECTAL CANCER

It is estimated that 74,630 women in the United States will be diagnosed with cancer of the colon or rectum in 2007 and an estimated 26,180 women will die of the disease by the end of the year, making colorectal cancer the third leading cause of cancer death among women. Black women have the highest incidence and death rates, followed by non-Hispanic White women. Colorectal cancer incidence rates have alternately risen and declined since 1975. Modest decreases in colorectal cancer mortality over the past decade have been largely attributed to the detection and removal of precancerous polyps, the early detection of tumors through screening, and improved treatments. However, the rate of colorectal screening remains low nationally and the potential benefit with broader utilization has yet to be achieved. Five-year survival rates are highest among Asian Pacific Islander (API) women and lowest among Black women. Lower rates of treatment with adjuvant therapy among Black patients may contribute to differences in cancer survival.

Gastrointestinal (GI) SPOREs. NCI supports four GI SPOREs, which focus research on cancers of the colon, rectum, and other digestive organs. SPORE researchers are exploring ways to use knowledge about the molecular genetic of colorectal cancer to improve early detection, prevention, and management of the disease. For example, researchers are using emerging genetic insights to devise new strategies for chemoprevention.

BIOLOGY

Two research studies identified colon cancer stem cells and showed that only a small subset of tumor cells from patients with colon cancer could initiate new tumors and sustain their growth. These few cancer stem cells, when transplanted into mice were able to form tumors that resembled the originals in patients, while other tumor cells could not. These findings suggest that targeting stem cells may be an effective strategy for preventive and therapeutic interventions.

RISK FACTORS

Diet. Researchers are investigating potential effects of various dietary factors on the risk for colorectal precancer and cancer. Data from the Polyp Prevention Trial show that participants who consumed the highest level of dry beans had a two-fold reduction in colorectal adenoma recurrence. A European study reported* that high levels of consumption of red and processed meat are associated with an increased risk of colorectal cancer, while high levels of fish consumption are associated with a decreased risk of the disease. Researchers from the WHI reported that taking daily supplements of calcium and vitamin D for 7 years did not reduce the risk of colorectal cancer in postmenopausal women. The supplements were modestly effective at preserving bone mass and preventing hip fractures. The researchers will follow this cohort of women for another 5 years.

Although selenium has protective effects against cancer in a variety of experimental systems, it is not clear whether this protection is a result of selenoproteins (proteins that include a selenocysteine residue) or if low molecular weight selenocompounds are responsible for this activity. However, a recent study provides the first evidence that both selenoproteins and low molecular weight selenocompounds have a role in colon cancer protection.

Diabetes. A large prospective cohort study of Singapore Chinese men and women found an overall increased risk of developing colorectal cancer in patients with diabetes. The researchers note that the diabetes and cancer risk link was not tied to obesity.

Genetic and Environmental Factors. NCI and others are identifying and characterizing a variety of genes and mutations associated with the development of colorectal cancer. Findings suggest a tumorigenic role of mutations

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in genes for serine kinases, threonine kinases, and *COX-2*, and an increased risk for sporadic colon cancer by inactivation of the gene *MGMT* by DNA methylation. A newly developed risk model provides clinicians with a tool to estimate the likelihood of individual patients carrying mutations in the *MLH1* and *MSH2* genes, the primary causes of HNPCC. Compared with the widely used Bethesda Guidelines, the new model would lead to the testing of fewer individuals, but would miss fewer mutation carriers.

Five hundred pairs of siblings who have had colon or rectal cancer and precancerous polyps were recruited for the CGN-sponsored Sibling Pair Colon Cancer Study (http://biostatistics.mgh.harvard.edu/siblingpair) for identification of genetic and environmental factors involved in colorectal cancer development. The investigations are being conducted in individuals where there is no known HNPCC or familial adenomatous polyposis (FAP) in the hope of identifying cancer genetic susceptibility regions. Data is currently being analyzed.

Colon Cancer Family Registries (CFRs). The Colon Cancer Family Registries (http://epi.grants.cancer.gov/CFR/about_colon.html) is an international registry system available to researchers who are planning to conduct population- and clinic-based interdisciplinary research with a main focus on the genetic and molecular epidemiology of colon cancer.

PREVENTION

NSAIDS. NCI and other are investigating the protective effect of NSAIDS on colorectal polyps and tumors. Researchers from the Adenoma Prevention with Celecoxib (APC) trial and another trial funded by Pfizer reported in April 2006 that daily use of the NSAID, celecoxib, significantly reduced the risk of precancerous polyps of the colon or rectum. NCI halted the APC trial in late 2004, after data analysis showed a 2.5-fold increased risk of major fatal and non-fatal cardiovascular events for participants taking the drug compared to those taking a placebo. In related research, results from the Polyp Prevention Trial suggest that individuals who are carriers of a particular genetic variant (*IL-10 –1082 G>A*) may not benefit from the chemoprotective effect of NSAIDs on adenoma polyp recurrence.

Statins. A large study has shown that people who took cholesterol lowering statins, the most frequently prescribed medications in the United States, for at least 5 years had a decreased risk of developing colorectal cancer. NCI is sponsoring a controlled, randomized clinical trial to rigorously test the efficacy of statins for prevention of colorectal cancer.

HPV. Researchers reported that HPV infection was found in more than half of 55 carefully examined tumor samples from patients with colorectal cancer and in none of 10 colorectal tissue samples from patients without cancer. However, further research is needed to establish a relationship between HPV infection and colorectal cancer. A vaccine for prevention of HPV infections responsible for 70 percent of cervical cancers has recently been approved by the FDA (see Cervical Cancer Prevention section).

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Colorectal Cancer Screening. NCI's Colorectal Cancer Screening initiative supports exploratory and developmental research aimed at improving the delivery, use, and short-term outcomes of colorectal cancer screening in primary care practice. This initiative also supports efforts by primary care practices to improve their capacity to collect patient, provider, practice, and clinical data and to conduct interventions that focus on increasing colorectal cancer screening.

Flexible sigmoidoscopy. Researchers from the PLCO Cancer Screening Trial report that patient acceptance of flexible sigmoidoscopy examination was high. Although diagnostic follow-up varied according to polyp size, cancer or adenoma detection rates met expectations. However, in another study partly funded by NCI, use of flexible sigmoidoscopy to screen women 50 years of age or older who are at average risk of colorectal cancer was

found to miss nearly two-thirds of advanced polyps. The investigators found that whereas pre-cancerous polyps in men tend to grow in the lower colon, in women the polyps tend to grow deeper in the colon, beyond the range of this screening technology.

Fecal Occult Blood Test (FOBT). According to a study from NCI and the CDC, many clinicians do not administer colorectal cancer screening with the in-home FOBT as recommended in the U.S. Preventative Services Task Force's 2002 guidelines. Many surveyed clinicians use the in-office FOBT which has not been proven to reduce colorectal cancer mortality. Furthermore, this and a second study report that many patients with positive FOBTs are not referred for colon exam. Other screening studies are comparing the immunochemical and traditional guaiac versions of the FOBT for accuracy in referring patients for colonoscopy.

Prognosis. Researchers report that improved colorectal cancer staging by lymphatic mapping may aid the selection of patients who are the best candidates for adjuvant chemotherapy. Lymphatic mapping entails injecting a dye at the primary tumor site just prior to surgical removal. The dye stains the sentinel lymph nodes, the first lymph nodes downstream from the tumor, which are removed and analyzed for metastatic tumor cells.

Researchers working with tumor samples from participants in a phase III clinical trail have developed a gene expression profiles assay that predicts response of rectal carcinomas to neoadjuvant chemoradiotherapy. The implementation of gene expression profiles for treatment stratification and clinical management of cancer patients will require validation in large, independent studies.

TREATMENT

Immune Therapy. Avastin and cetuximab are monoclonal antibodies used in conjunction with chemotherapy to treat metastatic colorectal cancer. NCI is supporting clinical trials to optimize the drug combinations used with these monoclonal antibodies. In 2006, the FDA approved another monoclonal antibody panitumumab (Vectibix), an EGFR inhibitor, for the treatment of metastatic colorectal cancer that has progressed despite standard chemotherapy. Approval was based on clinical trials* showing effectiveness in slowing tumor growth and, in some cases, reducing the size of the tumor.

A phase I study has reported promising findings for a treatment vaccine that targets carcinoembryonic antigen (CEA), a protein associated with a variety of cancers, including colorectal cancer. Forty percent of patients in the trial, including some colorectal cancer patients, experienced stable disease when treated with the vaccine in conjunction with a compound known to enhance vaccine efficacy. Further clinical research is needed to determine survival outcomes with this form of therapy.

SURVIVORSHIP

The results of two prospective observational studies showed that patients with early to late stage colorectal cancer (but not distant metastases) who engaged in regular activity after diagnosis had a decreased likelihood of cancer recurrence and mortality of 40 to 50 percent or more, compared with patients who engaged in little or no activity. These findings held true regardless of levels of physical activity before cancer diagnosis or other risk factors for recurrence.

HEALTH DISPARITIES

Screening. Researchers report that colorectal cancer screening rates are rising for both men and women in the United States, driven by a sharp increase in the use of colonoscopy. However, less than half of those eligible undergo screening, and screening rates are higher in men than women. Furthermore, screening use remains lower

* Research studies denoted with an asterisk may not have received NCI funding. However, these advances were included because they are significant contributions to research on cancers in women.

for those of Hispanic ethnicity, at lower education levels, lacking health insurance, without a usual source of health care, and those who have not talked with a doctor in the past year.

Treatment. According to a large prospective study, the use of adjuvant chemotherapy in patients with stage III colon cancer has increased significantly since recommendations from a 1990 NIH consensus conference advised clinicians to implement the practice. However, nearly one-third of patients received surgery only for treatment, particularly female and elderly patients. Another study* found that 11 percent fewer Black than White patients with colorectal cancer received adjuvant chemotherapy. Researchers analyzing Medicaid-linked SEER data found that hospitalization due to side effects from the 5-fluorouracil family of drugs and low social or psychological support are the factors most closely related to whether patients with stage III colon cancer complete adjuvant chemotherapy. The authors suggest testing whether interventions to improve social and physical support for patients during treatment would improve adherence. Yet another study* concluded that non-English-speaking patients with colorectal cancer were less satisfied with their care than English-speaking patients.

Access to Care. The NCI CRCHD is administering development of an innovative Patient Navigator Research Program (http://crchd.cancer.gov/pnp/pnrp-index.html), focusing on four cancers for which screening tests are available: breast, cervical, prostate and colorectal. (See Cancer Control, Survivorship, and Outcomes research in the Breast Cancer section of this report.)

* Research studies denoted with an asterisk may not have received NCI funding. However, these advances were included because they are significant contributions to research on cancers in women.

AIDS-ASSOCIATED MALIGNANCIES

AIDS and HIV infection continue to be major public health concerns. From 1981 to 2001, 929,985 cases of AIDS were reported to the CDC. Based on CDC estimates, the number of HIV/AIDS cases decreased 17 percent among females between 2001 and 2005. In 2005, the estimated rate of HIV/AIDS cases was 20.2 per 100,000 and about 26 percent of these were in females. There were about 14.9 per 100,000 cases of AIDS, 27 percent of which were in females. About 80 percent of HIV/AIDS transmission among women in 2005 occurred by high risk heterosexual activity. 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. Approximately 476,095 persons are currently living with HIV infection or AIDS in the 33 states with confidential name-based reporting. Of those, 27 percent were adult and adolescent women. Minorities accounted for 79 percent of these women, including 64 percent Black and 15 percent Hispanics.

The longer life expectancy of HIV positive people on HAART, who are living with partially restored immune function, may increase the cumulative risk of developing both AIDS-defining and non-defining cancers. The AIDS-defining malignancies are non-Hodgkin's lymphoma (NHL), cervical cancer, anal cancer, and Kaposi's sarcoma (KS). The 23 fold increased risk of NHL is particularly concerning since this cancer ranks sixth in overall female cancer incidence and mortality. Although HIV-infected women who have initiated HAART experience significant reductions in overall cancer risks, NHL incidence remains higher in this population compared to the HIV uninfected U.S. population. KS, although a rare cancer, is 200 times more likely to occur in HIV infected women than in uninfected women. Some studies have found the risk of cervical neoplasia to be five times higher in women with HIV infection than in HIV negative women, due to a higher prevalence and persistence of oncogenic HPV infection. The prognosis for cervical cancer is also poorer for HIV positive than for HIV negative women. Women infected with both HIV and HPV have a 6.8 fold greater risk of invasive anal cancer than HIV negative, HPV positive women. And, HIV infected women have been found to have high rates of infection with oncogenic tumor viruses, including hepatitis C and human herpes virus 8.

Lymphoma SPORE. The NCI lymphoma SPORE located at John Hopkins University (http://spores.nci.nih.gov/current/lymphoma/lymphoma_docs/lym-ambinder.html) is investigating the molecular epidemiology of AIDS-related NHL (AIDS-NHL). These researchers seek to identify immune-related molecular changes that precede AIDS-NHL development and molecular markers for AIDS-NHL risk assessment, as well as treatment strategies for high-risk individuals.

AIDS Malignancy Program (AMP). NCI's AMP, http://ctep.cancer.gov/resources/aidsmalignancy/, provides coordination and programmatic support of AIDS associated-malignancy research across NIH to provide opportunities for an integrated, multidisciplinary investigations.

Centers for AIDS Research (CFAR). The trans-NIH CFAR (http://www.niaid.nih.gov/research/cfar) program provides administrative and shared research support to synergistically enhance and coordinate high quality AIDS research projects, both nationally and internationally. Core facilities provide expertise, resources, and services not readily obtained through more traditional funding mechanisms. Researchers at 20 CFARs study the natural history and pathobiology of HIV-related malignancies in diverse populations in men, women, and children, and investigate the role of sex and gender in AIDS therapy and prevention through collaborative studies in women and girls.

RISK FACTORS

Women's Interagency HIV Study (WIHS) (https://statepiaps.jhsph.edu/wihs)**.** Since 1995, NCI has co-funded the WIHS to support malignancy studies in this National Institute of Allergy and Infectious Diseases (NIAID)/NICHD/NIDA initiative, the largest U.S. study of HIV infection in women. A recent WIHS study estimated the risk of and risk factors for progression in HIV infected women with abnormal cervical cytology but

negative colposcopy. They found that the risk of progression is higher in HIV infected women, but the absolute risk is low and becomes nonsignificant after controlling for HPV risk type, ethnicity, and colposcopic findings.

Another WIHS study showed that in HIV-positive women, the combination of increasing plasma HIV RNA level and decreasing CD4 cell count may be associated with HPV reactivation (e.g., in sexually inactive women). The more moderate association between HIV coinfection and HPV persistence could partly explain why cervical cancer rates have not reached more epidemic proportions in HIV-positive women.

Infectious agents Viral Epidemiology Branch (VEB). The VEB conducts multidisciplinary studies of carefully selected domestic and foreign populations, with the goal of clarifying the relationship of infectious agents, especially viruses, to human cancer and other conditions. Investigators have reported a reduced risk of breast and post-menopausal endometrial cancer among women with AIDS. These findings are being followed up in studies to clarify the relationship of retrovirus infection and immunity to breast cancer.

Anal Disease. Preliminary data from a CFAR study addressing risk factors for anal disease in HIV-infected women suggests that anal HPV infection exceeds cervical HPV infection in this population.

Specimen Resources. The AMP-supported AIDS and Cancer Specimen Resource (ACSR), http://acsr.ucsf.edu, catalyzes epidemiological and pathogenesis studies of genetic and environmental risks for development of AIDS-associated cancer by enhancing collection, storage, and effective utilization of specimens from WIHS participants. The ACSR provides access to over 140,000 specimens and associated clinical data collected from cohort studies, clinical trials, and other research.

PREVENTION

The 2006 International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies (ICMAIO), was sponsored by AMP, NCI's Office of International Affairs, NCI Office of Women's Health, and HHS Office on Women's Health. Conference presentations highlighted HPV pathogenesis, molecular epidemiology of HPV sub-types associated with HIV in developing countries, and the potential impact of the newly approved HPV vaccine and other preventive strategies in reducing the risk of HPV-associated cancers in HIV-infected women.

EARLY DETECTION, DIAGNOSIS, AND PROGNOSIS

Cervical Cancer Screening. WIHS researchers recently assessed the incidence of squamous intraepithelial lesions (SILs) in HIV-seropositive women with normal cytology results. Their findings suggest that the recommended cervical screening interval of 3 years in healthy women aged 30 years or older who have normal cytology results and a negative oncogenic HPV test, may also be appropriate for HIV infected women. However, the investigators note the need for a clinical trial to evaluate this strategy.

TREATMENT

Developing Novel Therapies. NCI researchers are searching for more effective AIDS therapies that will reduce the incidence of AIDS-related malignancies and for treatments that will improve survival of patients with these malignancies.

AIDS Malignancy Consortium (AMC). The NCI-funded AMC conducts treatment clinical trials in HIV-associated malignancies. Ongoing trials include investigation of combined modality therapy plus Erbitux in HIV-associated anal carcinoma, valproic acid in patients with KS, Gleevec in patients with KS, and a high-dose, short-course chemotherapy regimen for HIV-associated Burkitt's and Burkitt's-like lymphoma. AMC is also developing studies to assess the safety and efficacy of HPV vaccines in women infected with HIV.

HIV and AIDS Malignancy Branch (HAMB). NCI's intramural HAMB (http://ccr.cancer.gov/labs/lab.asp?labid=63) conducts translational research on HIV infection and AIDS-related malignancies to develop novel therapies for

AIDS and AIDS-related malignancies and to understand the effects of these therapies on disease pathogenesis. HAMB investigators were responsible for the early development of darunavir, an HIV protease inhibitor that was recently approved by the FDA as an anti-HIV therapy. Now, results from an early HAMB clinical trial show a promising effect of interleukin-12 (IL-12), which can act as both an immunostimulator and an antiangiogenesis agent, for treatment of patients with AIDS-related KS.

Nevirapine. Investigators have shown that treating South African women with a single dose of the drug, nevirapine (sdNVP), used to prevent mother-to-child transmission, induced mutations conferring resistance to this drug in approximately 70% of the study participants. These findings highlight the need for studies assessing the impact of sdNVP on the efficacy of subsequent antiretroviral therapy containing nevirapine or similar agents.

TRAINING

AIDS International Training and Research Program (AITRP). NCI is a co-sponsor of the AITRP (http://www.fic.nih.gov/programs/training_grants/aitrp/index.htm), which supports HIV/AIDS-related research training to strengthen the capacity of institutions in low- and middle-income countries.

Selected Program Announcements (PA/PAR/PASs) and Requests for Applications (RFAs) Relevant to Women's Health, FY 2005–2006

PA-05-086, PA-06-282 (NCI, NIA)
Stem Cells and Cancer

This funding opportunity is intended to promote research on all aspects of tumor stem cell biology and on the genes and proteins responsible for the tumor stem cell phenotype. Studies on the characterization of tumor stem cells from the broad spectrum of solid and liquid tumors not already examined, markers potentially shared by tumor stem cells and normal stem cells, and the biochemical and molecular regulation of normal and tumor stem cell function are encouraged.

PA-05-125
Diet-Induced Changes in Inflammation as Determinants of Colon Cancer

The goal of this PA is to foster research that will identify and characterize diet-induced changes in inflammation linked with colon cancer risks. The focus should be on defining the physiological significance of diet in modulating inflammatory processes that may be linked to colon cancer development.

PA-06-031 (STTR), PA-06-032 (SBIR)
Image-Guided Cancer Interventions

This PA supports the development and clinical validation of systems for Image-Guided Interventions (IGIs) for cancer that will foster: the development and optimization of fully integrated cancer imaging, monitoring, and therapy systems; validation through clinical evaluations; development of multiple prototype for multi-site clinical evaluations; and partnerships among small businesses, large businesses, and academic clinical centers, to reach the research goals.

PA-06-277 (NCI, NIEHS, ODS)
In Utero Exposure to Bioactive Food Components and Mammary Cancer Risk

The PA supports applications on in-utero exposures that are determinants of some cancers occurring in children and young adults. Studies that apply new high-throughput genomic, epigenomic, proteomic, and metabolomic technologies or genetically engineered animal models to determine how dietary and/or environmental chemical exposures in utero influence adult breast cancer susceptibility are encouraged.

PA-06-280, PA-06-281
Understanding the Effects of Emerging Cellular, Molecular, and Genomic (CMG) Technologies on Cancer Health Care Delivery

This PA supports health services research on the use of CMG technologies in cancer care related to quality of care; organizational barriers and change factors in use; cost and cost-effectiveness; disparities in access and efficacy; monitoring of cross-sectional patterns of care and time trends; impact on existing standards of care; and influence on cancer outcomes such as incidence, progression, mortality, survival, and quality of life.

PA-06-289, PA-06-290
Immunoregulation of Gastrointestinal Carcinogenesis

These PAs focus on the role of the mucosal immune system in initiating and maintaining inflammatory responses leading to the development of pre-malignant and malignant gastrointestinal cancers. Research efforts should lead to an understanding of how immune responses participate in gastrointestinal carcinogenesis.

PA-06-297 (NCI, NIDCR)
Protein Biomarkers of Infection-Associated Cancers

This PA encourages identification of proteomic markers for risk assessment and early detection in individuals exposed to infectious agents that have been linked to cancer. Agents of interest include HPV, hepatitis B and C viruses, EBV, and Simian Virus 40. Projects on early cervical, lung, and colon cancers among HIV patients, and bacterial etiology in cancer are encouraged.

PA-06-299
Exploratory Studies in Cancer Detection, Diagnosis, and Prognosis

The objective of this PA is to promote evaluation of new molecular or cellular characteristics of pre-malignant cells or tumors or the development of assays that will be useful for cancer detection, diagnosis, and/or prognosis. Translational studies that identify promising new means for cancer detection and diagnosis and determine whether potential clinical utility justifies further investment are encouraged.

PA-06-304 (NCI, AHRQ)
Studies of the Economics of Cancer Prevention, Screening, and Care

This PA invites applications for research directed at increasing the knowledge base in the area of the economic aspects of cancer prevention, screening, and care in order to promote the optimal design of cancer prevention and control trial studies and interventions and facilitate the formulation of effective health care policy related to cancer prevention and control.

PA-06-305
Decision Making in Cancer: Single-Event Decisions

This PA invites applications for research projects that will enhance understanding of human decision-making processes so that individuals can make more informed and satisfying choices regarding their health, related to cancer prevention, detection, treatment, survivorship, or end-of-life care.

PA-06-306, PA-06-348 (NCI, NIDDK, OBSSR, NHLBI, NIBIB, NIDA)
The Effect of Racial and Ethnic Discrimination/Bias on Health Care Delivery

The purposes of this PA are: (1) To improve the measurement of racial/ethnic discrimination in healthcare delivery systems (2) to enhance understanding of the influence of racial/ethnic discrimination in healthcare delivery; and (3) to reduce the prevalence of racial/ethnic health disparities through the development of interventions to reduce the influence of racial/ethnic discrimination on healthcare delivery systems in the United States.

PA-06-337 (NCI, NIDA, NIAAA)
Decision Making in Health: Behavior Maintenance

The purpose of this PA is to expand our knowledge of basic decision-making processes underlying the initiation and long-term maintenance of healthy lifestyle behaviors that may reduce one's risk of cancer and other chronic diseases.

PA-06-338 (NCI, NIDCR)
Research on Malignancies in AIDS and Acquired Immune Suppression

The goal of this funding announcement is to encourage applications ranging in scope from basic science through molecular epidemiology to preclinical studies and including but not limited to (1) developing and using animal and cell culture models to study disease pathogenesis; (2) discovering and characterizing new viral and microbiological agents that act as co-factors in tumor promotion or progression; (3) developing and using predictive models for the preclinical evaluation of new therapies against AIDS-related malignancies; (4) developing preclinical applications to translate basic knowledge of AIDS-related malignancies toward the development of new treatments; (5) defining

the molecular epidemiology of HIV-associated cancers and their pre-neoplastic conditions; and (6) discovering, developing, and using biomarkers of cancer risk, progression, or response to treatment.

PA-06-349, PA-06-350
Memory T Lymphocytes in Cancer Immunology

These PAs are intended to focus research on memory T lymphocytes and the cells and molecules with which they interact. The overarching objective is to ultimately improve the prospects for the development and application of vaccines and immunotherapies that can be used to successfully prevent and treat cancers in humans.

PA-06-359, PA-06-360
Exfoliated Cells, Bioactive Food Components, and Cancer

This PA promotes innovative preclinical and clinical research to evaluate the utility of using exfoliated cells to monitor variation in dietary intakes of bioactive food components thought to be involved with cancer prevention. Potential areas of investigation include studying the effect of individual dietary components on molecular or biochemical processes and predicting the anticancer responses in surrogate samples, blood, and its constituents and target tissues.

PA-06-361 (NCI, NIDA)
Testing Tobacco Products Promoted to Reduce Harm

This PA encourages multidisciplinary research on the chemical composition, use, exposure to toxic agents, addictive properties, differential toxicity, and individual and public health impact of potential reduced-exposure tobacco products.

PA-06-385, PA-06-386 (NCI, AHRQ)
Cancer Surveillance Using Health Claims-Based Data

NCI, in partnership with AHRQ, supports research directed at the use of health claims data for cancer surveillance, including studies of cancer detection, treatment, and/or outcomes.

PA-06-398, PA-06-399
Novel Technologies for In Vivo Imaging

This PA invites applications for the development and delivery of novel image acquisition or enhancement technologies and methods for biomedical imaging and image-guided interventions and therapy.

PA-06-400 (NCI, NINR, NCCAM)
Developmental Projects in Complementary Approaches to Cancer Care

The intent of this PA is to encourage the development of basic and clinical (prevention, therapeutic, and palliative) cancer research in complementary approaches and to facilitate communication and collaboration between practitioners in complementary approaches and the conventional cancer research communities.

PA-06-404, PA-06-405
Studies of Energy Balance and Cancer in Humans

NCI invites applications that focus on factors affecting energy balance and mechanisms influencing cancer risk, prognosis, and quality of life. Projects may include new analyses of existing datasets to additional collection of data and biological specimens in ongoing investigations.

PA-06-412, PA-06-413, PA-06-414 (NCI, NIAAA, NIDDK, ODS)
Diet, Epigenetic Events, and Cancer Prevention

This PA is intended to promote preclinical and clinical research to determine how diet, dietary factors, and dietary supplements impact epigenetic processes involved in cancer prevention. Research supported by this initiative could address how bioactive food components regulate epigenetic events for cancer prevention, how bioactive food

components might alter aberrant epigenetic patterns or events and restore gene function, and how these components might circumvent or compensate for genes and pathways that are altered by epigenetic events.

PA-06-510 (NCI, NCCAM)
Exploratory/Developmental Grant for Clinical Studies of Complementary and Alternative Medicine

NCI and NCCAM invite high quality exploratory/developmental clinical research grant applications that focus on complementary alternative medicine (CAM) approaches related to cancer symptoms and side-effects of cancer treatment as well as survivorship. It is anticipated that these pilot studies will generate supporting preliminary clinical data that can be used to support larger clinical studies.

PA-07-022, PA-07-021
Development, Application, and Evaluation of Prediction Models for Cancer Risk and Prognosis

The purpose of this PA to encourage clinicians, epidemiologists, geneticists, statisticians, and translational cancer control and prevention researchers to improve existing models for cancer risk, prognosis, or response to therapy by developing innovative research projects that: use existing data; develop new models for cancer risk and prognosis; and validate new models and evaluate their utility in research and clinic settings.

PA-07-173 (NCI, NIDCR)
Research on Malignancies in AIDS and Acquired Immune Suppression

The goal of this funding announcement is to encourage applications ranging in scope from basic science through molecular epidemiology to preclinical studies and including but not limited to (1) developing and using animal and cell culture models to study disease pathogenesis; (2) discovering and characterizing new viral and microbiological agents that act as co-factors in tumor promotion or progression; (3) developing and using predictive models for the preclinical evaluation of new therapies against AIDS-related malignancies; (4) developing preclinical applications to translate basic knowledge of AIDS-related malignancies toward the development of new treatments; (5) defining the molecular epidemiology of HIV-associated cancers and their pre-neoplastic conditions; and (6) discovering, developing, and using biomarkers of cancer risk, progression, or response to treatment.

PAR-05-042
Specialized Programs of Research Excellence (SPOREs) in Human Cancer for Year 2005-2006

SPOREs should conduct translational research in the prevention, etiology, screening, diagnosis, and treatment of organ-specific cancers. Each SPORE is expected to conduct research that will have immediate impact on reducing incidence and mortality of human cancer and must include a minimum of four translational research projects, cores, developmental research and career development programs.

PAR-06-451
Quick-Trials for Novel Cancer Therapies: Exploratory Grants

This Announcement will continue to support scientific, technological, clinical, and logistical needs in novel cancer therapy development.

PAS-06-466, PAS-06-467 (NIA, NIDDK, NCI, NIEHS)
The Role of Nuclear Receptors in Tissue and Organismal Aging

This PA supports projects aimed at understanding the role of nuclear hormones and their regulation in a number of human malignancies (e.g. thyroid, lung, colon, endometrium, ovary, and breast) and includes research on the role of the coregulators in regulating transcription, influencing epithelial-stromal interactions during cancer progression contributing to hormone resistance, as well as in determining therapeutic response.

RFA-TW-06-006 (FIC, NCI)
International Tobacco and Health Research and Capacity Building Program

This RFA solicits research to address the burden of tobacco consumption in low- and middle-income nations by (1) pursuing observational, intervention and policy research of local relevance; and (2) building capacity in these regions in epidemiological and behavioral research, prevention, treatment, communications, health services and policy research.

RFA CA-03-00
Nutritional Modulation of Genetic Pathways Leading to Cancer

NCI funds four research centers as part of the *Nutritional Modulation of Genetic Pathways Leading to Cancer* U54 Cooperative Agreement. The goal of this initiative is to expand and facilitate fundamental research that will define the molecular basis by which dietary components influence cancer prevention

RFA-CA-06-011
Comprehensive Minority Institution/Cancer Center Partnership (P20)

The NCI invites applications for partnerships and feasibility studies between Minority-Serving Institutions and NCI-designated Cancer Centers (or groups of Centers) to develop a stronger national cancer program aimed at understanding the reasons behind the significant cancer disparities and impact on minority populations.

RFA-CA-06-014
Tumor Microenvironment Network (TMEN) (U54)

This RFA supports the NCI TMEN, which consists of inter-connected, multidisciplinary teams of investigators and collaborative groups that will delineate mechanisms of tumor-stroma interactions in human cancer. Up to six research programs will be supported, each consisting of multidisciplinary teams with expertise in specific tumor site(s) and using human cancer samples and/or well-defined vertebrate models.

RFA-CA-06-015
Exploratory Grants for Increasing the Utilization and Impact of the National Cancer Institute's Cancer Information Service (R21)

The purpose of this RFA is to promote research to develop and test national, regional, or community-based interventions that increase the use and assess the impact of scientifically accurate and up-to-date cancer information delivered through existing CIS resources.

RFA-CA-06-505
Cancer Research Network (U19)

The goal of this RFA is to increase scientific knowledge in cancer epidemiology, risk factors, prevention, early detection, diagnosis, prognosis, treatment, and end-of-life care in the context of community-based health care delivery.

RFA-CA-07-001 (R01), RFA-CA-07-006 (SBIR), RFA-CA-07-007 (STTR) RFA-CA-07-015 (R21), RFA-CA-07-016 (R33)
Innovative Technologies for Molecular Analysis of Cancer

The NCI invites applications to develop cancer-relevant molecular analysis technologies, including detection of alterations of genomic DNA; measurement of gene expressions and products; analysis and detection of gene and/or cellular products; identification and characterization of exogenous infectious agents in cancer; and assaying the function of signal transduction networks involved in cancer.

RFA-CA-07-004
Small Animal Imaging Resource Program

These programs support (1) imaging technologies for small animals, that provide information related to malignancy in vivo; (2) new imaging technologies appropriate for small animals; (3) the development of probes for the imaging technologies provided; (4) small animal anesthesia and care; and (5) training for professional and technical personnel in cancer-related small animal imaging

RFA-CA-07-005
Advanced Proteomic Platforms and Computational Sciences for the NCI Clinical Proteomic Technologies Initiative

The NCI invites applications in proteomic technology to be applied to the measurement of proteins and peptides of interest in clinical cancer studies, and supports two focus areas: (1) the development of technology for protein and peptide detection, recognition, measurement, and characterization in biological fluids and (2) computational, statistical, and mathematical approaches for the analysis, processing, and exchange of large proteomic data sets.

RFA-CA-07-014
Cancer Genome Characterization Centers

This RFA is designed to establish a collaborative group of multidisciplinary Cancer Genome Characterization Centers (CGCCs) as part of The Cancer Genome Atlas (TCGA) Pilot Project. The Centers will use genomic and/or epigenomic analysis technologies to pioneer the systematic, high-resolution, comprehensive characterization of cancer-related genomic alterations.

RFA-CA-07-021 (R21), RFA-CA-07-029 (R43, R44), RFA-CA-07-030 (R41, R42) (NCI, NHGRI)
Development of Advanced Genomic Characterization Technologies

This RFA is a component of the Cancer Genome Atlas Pilot Project and solicits research projects to develop highly innovative and novel genomic analysis technologies to provide new insights and understanding into the role of genetic alterations in cancer.

RFA-CA-07-002 (SBIR), RFA-CA-07-009 (STTR), RFA-CA-07-017 (R21), RFA-CA-07-018 (R33), RFA-CA-07-019 (R21, R33)
Application of Emerging Technologies for Cancer Research

NCI invites projects to evaluate the usefulness of emerging molecular technologies that are ready for initial application to clinical or biological questions in cancer research. Projects should demonstrate that the technology is robust and yields reproducible measurements.

RFA-CA-07-025
Community Clinical Oncology Program (CCOP)

The CCOP network is designed to increase the involvement of community oncologists and their patients in NCI-sponsored clinical trials; involve a wider segment of the community in cancer clinical trials, including minorities, women, and other underserved populations; and accelerate the transfer of knowledge gained from clinical trials to community oncology practices.

RFA-CA-07-026
Minority-Based Community Clinical Oncology Program

The objective of this initiative is to bring cancer clinical trials to minority individuals in their own communities and to involve physicians in these communities in NCI-approved clinical trials in an effort to reduce health disparities in minority populations.

SELECTED MEETINGS OF INTEREST

(Sponsored or co-sponsored by NCI, FY2005–2006)

The 10th International Conference on Malignancies in AIDS and Other Acquired Immunodeficiencies
(Bethesda, MD; October 16-17, 2006)

Cancer Survivorship: Embracing the Future
(Bethesda, MD; October 4-6, 2006)

Intra-peritoneal Chemotherapy for Ovarian Cancer
Symposium at the International Conference on Cancer Nursing
(Toronto, Canada; September 27 - October 1, 2006)

Consensus Guidelines for Management of Women with Cervical Abnormalities
(Bethesda, MD; September 17-19, 2006)

Personalized Breast Cancer Therapy
Symposium at the 25th Congress of The International Association of Breast Cancer Research (IABCR) Conference
(Montreal Canada; September 15-18, 2006)

Second Biennial Workshop to Increase Diversity in Research Funding
(Palm Desert, CA; September 6-8, 2006)

Team Up: Cancer Screening Saves Lives 2006 National Meeting
(Charleston, SC; August 1-4, 2006)

Health Disparities Research Methods Training
Symposium in Conjunction with the IUCC World Conference and the 13th World Conference on Tobacco OR Health
(Washington, DC; July 12, 2006)

NCI Advocacy Summit on Listening and Learning Together: Building a Bridge of Trust
(Bethesda, MD; June 19-20, 2006)

NIH State-of-the-Science Conference on Tobacco Use: Prevention, Cessation, and Control
(Bethesda, MD; June 12-14, 2006)

3rd Annual Uterine Cancer Biology Symposium
(St. Louis, MO; May 13, 2006)

NCI Symposium on State-of-the-Science Health Communication
(Bethesda, MD; May 10, 2006)

Progesterone Receptor Modulators and the Endometrium: Changes and Consequences
(Bethesda, MD; April 7-8, 2006)

NCI Workshop to Assess the Evidence for a Randomized Clinical Trial on Weight Control and Prevention of Breast Cancer Recurrence
(Rockville, MD; March 15-16, 2006)

Enhancing Interactions To Reduce Cancer Health Disparities
(Bethesda, MD; November 17-18, 2005)

Ovarian Cancer: Prevention & Detection of the Disease & Its Recurrence
(Pittsburgh, PA; October 24-25, 2005)

9th International Conference on Malignancies in AIDS and Other Immunodeficiencies
(Bethesda, MD; Sept. 26-27, 2005)

Tobacco Control Policies: Do They Make a Difference for Low SES Women and Girls?
(Bethesda, MD; Sept. 22-23, 2005)

Transplacental Exposure to Nucleoside Analogs: Mitochondrial Damage and Fetal Health Symposium at the 9th International Conference on Environmental Mutagens
(San Francisco, CA; September 3-8, 2005)

Breast Cancer, Prevention and Gynecologic Malignancies Combined Faculty Retreat on Prevention
(Cumberland, MD; July 20-22, 2005)

Diet and Communication: What Can Communication Science Tell Us About Promoting Optimal Dietary Behavior?
(Bethesda, MD; July 14-15, 2005)

4th International Conference on Cervical Cancer
(Houston, TX; May 19-22, 2005)

Helene Harris Memorial Trust 10th International Forum on Ovarian Cancer
(Washington, DC; April 5-7, 2005)

Workshop on Women and Cancer at the 2nd Clinical Health Psychology Institute on Women's Health
(Washington, DC; April 1-2, 2005)

4th Annual Intraductal Approach to Breast Cancer Symposium
(Santa Barbara, CA; March 10-13, 2005)

KEY WORDS

BREAST CANCER

Trans-NCI Breast Premalignancy Program, mouse models, HER2 , Herceptin® (trastuzumab), stem cells, ductal lavage, Consortium of Cohorts, Cancer Genetic Markers of Susceptibility, registry(ies), genetic factors, environmental factors, lifestyle, reproductive factors, diet, Women's Intervention Nutrition Study, physical activity, Women's Healthy Eating and Living (WHEL) Study, hormone therapy, DES, Long Island Breast Cancer Study Project (LIBCSP), DDT, radiation, Breast Cancer and Environment Research Centers (BCERC), Study of Tamoxifen and Raloxifene (STAR), selective estrogen receptor modulators (SERMs), genistein, statin, Simvastin, bexarotene, NSAID, sulindac, grape seed proanthocyanidin extract, prophylactic Mastectomy, BRCA1, BRCA2, prophylactic oophorectomy, Breast Cancer Surveillance Consortium (BCSC), Gail Model, Digital Mammography Imaging Screening Trial (DMIST), MRI, ultrasound, PET, SPECT, sonography, Trial Assigning Individualized Options for Treatment (Rx) (TAILORx), Oncotype DX™, gene expression profile(s), aromatase inhibitors (AIs), Armidex® (anastrozole), letrozole (Femara ®), estrogen receptors, lymph nodes, cyclophosphamide, methotrexate, 5-fluorouracil, doxorubicin, taxane, Gleevec, bortezomib (Velcade®), medroxyprogesterone, metastasis suppressor gene, bevacizumab (Avastin), paclitaxel (Taxol), lymphedema, screening, survivorship, NCI Centers of Excellence in Cancer Communications Research (CECCR), health disparities, Patient Navigator Research Program

CERVICAL CANCER

human papillomavirus (HPV), Guanacaste Study of HPV Natural History in Costa Rica, Portland Kaiser Permanente Cohort Study, contraceptive, reproductive, diet, smoking, The Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED), DES, HPV Vaccine, condom, carrageenan, ASCUS-LSIL Triage Study (ALTS), Human Telomerase Gene (TERC), topotecan hydrochloride (Hycamtin), cisplatin, treatment-related side effects, Health Information National Trends Survey (HINTS), psychosocial issues, sexuality issues, health disparities, Pap testing, "TEAM-UP: Cancer Screening Saves Lives," Patient Navigator Research Program

OVARIAN CANCER

screening, biomarkers, CA-125, transvaginal ultrasound, platinum/taxane-based treatments, Cancer Genome Atlas (TCGA), mouse models, endometrial ovarian cancer (EOC), BRCA1, BRCA2, stem-like cells, Mullerian Inhibiting Substance (MIS), optical imaging, tumor foci, reproductive factors, demographic factors, lifestyle factors, oral contraceptives, pregnancy, breast fed, tubal ligation, hysterectomy, hormone therapy, Lynch II syndrome, estrogen, registries, quality of life, proteomic(s), mesothelin, National Ovarian Cancer Early Detection Program: Screening and Genetic Study, Ovarian Pap Test, Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) Trial, carboplatin, cisplatin, alkylating agents, paclitaxel, intraperitoneal chemotherapy, Velcade, docetaxel (Taxotere®), erlotinib (Tarceva®), gemcitabine (Gemzar®), liposomal doxorubicin, nitrocamptothecin, oxaliplatin (Eloxatin®), sorafenib (BAY 43-9006), Avastin, TLK286, topotecan, immunotoxin-SS1P, fertility issues

ENDOMETRIAL CANCER

molecular markers, estrogen, progesterone, SERMs, tamoxifen, raloxifene, Arzoxifene, mouse models, specimen resources, Gynecologic Oncology Group (GOG), obesity, age, physical activity, hereditary nonpolyposis colon cancer (HNPCC), Lynch Syndrome, diabetes, smoking, complex carbohydrates, aromatase inhibitors, nutrition, progestins, ethinyl estradiol, norgestrel, hysterectomy, bilateral salpingo-oophorectomy, adjuvant chemotherapy, fertility issues, cisplatin, doxorubicin, radiation therapy, carboplatin, paclitaxel therapy, Herceptin, Avastin, sorafenib, temsirolimus (CCI-779), 852A, health disparities, socioeconomic factors, biologic factors, cultural factors

LUNG AND OTHER TOBACCO-RELATED CANCERS

Smoking, tobacco, lung, cervical, ovarian, colorectal, breast, leukemia, bladder, esophagus, kidney, larynx, oral cavity, pancreas, stomach, Lung Cancer Program (LCP), CISNET, Transdisciplinary Tobacco Use Research Centers (TTURCs), estrogen receptors (ER), ER antagonists, gender differences, Cancer Genome Atlas (TCGA), tobacco, PLCO, Shanghai Women's Health Study, second hand smoke, diet, phytoestrogen(s), genetic factors, proteomics, addiction, National Health Interview Survey (NHIS), tobacco control, "Quit Now" Challenge, "Quit to Live: Fighting Lung Cancer," "Helping Young Smokers Quit," reduced-exposure tobacco products, monographs, ASSIST, Community Intervention Trial for Smoking Cessation (COMMIT), TTURC, bupropion, National Lung Screening Trial (NLST), low-dose spiral computed tomography, chest x-rays, NCI Imaging Archive (NCIA), PET, metagene, microRNAs (miRNAs), ERCC1, cisplatin, EGFR, gefitinib (Iressa®), Tarceva®, Avastin, sorafenib, cetuximab (Erbitux®), AKT, phosphatidylinositol ether lipid analogs (PIAs), ErbB3, erlotnib, health disparities, TReND, SES

COLORECTAL CANCER

SPOREs, stem cells, diet, Polyp Prevention Trial, dry beans, red and processed meat, fish, WHI, calcium, vitamin D, selenium, diabetes, genetic and environmental factors, serine kinases, threonine kinases, COX-2, MGMT, MLH1, MSH2 HNPCC, Sibling Pair Colon Cancer Study, registries, NSAIDS, Adenoma Prevention with Celecoxib (APC) trial celecoxib, Polyp Prevention Trial, (IL-10 –1082 G>A), statins, HPV, screening, flexible sigmoidoscopy, PLCO Cancer Screening Trial, Fecal Occult Blood Test (FOBT), lymphatic mapping, immune therapy, Avastin, cetuximab, panitumumab (Vectibix), EGFR, carcinoembryonic antigen (CEA), survivorship, physical activity, health disparities, access to care, Patient Navigator Research Program

AIDS-ASSOCIATED MALIGNANCIES

AIDS, HIV highly active antiretroviral therapy (HAART), non-Hodgkin's lymphoma (NHL), cervical cancer, anal cancer, Kaposi's sarcoma (KS), HPV, oncogenic tumor viruses, hepatitis C, human herpes virus 8, AIDS Malignancy Program (AMP), Centers for AIDS Research (CFAR), Women's Interagency HIV Study (WIHS), cervical cytology, colposcopy, plasma HIV RNA, CD4 cell count, Viral Epidemiology Branch (VEB), specimen resources, HPV vaccine, AIDS Malignancy Consortium (AMC), Erbitux, valproic acid, Gleevec, HIV-associated Burkitt's and Burkitt's-like lymphoma, HIV and AIDS Malignancy Branch (HAMB), darunavir, protease inhibitor, anti-HIV therapy, interleukin-12 (IL-12), immunostimulator, antiangiogenesis, nevirapine, AIDS International Training and Research Program (AITRP)