National Cancer Institute

The Nation's Progress in Cancer Research

An Annual Report for 2004

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health


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Director's Message

Every day in the newspaper and on television, Americans learn about new drugs and ways to prevent cancer through lifestyle changes. We also learn every day about the many who still suffer and die from the diseases we call cancer. This report is a celebration of some of the successes that, in the course of just one year, have accelerated our progress toward achieving our Challenge Goal to the Nation to eliminate the suffering and death due to cancer by 2015. For some of these advances, realizing their benefits will take more time. Others, however, will have an immediate effect.

The year 2004 was pivotal in many ways for cancer research, as we continued to reap the benefits of the new molecular technologies that are enabling us to understand cancer as a biological process—and a process that can be interrupted and controlled. The National Cancer Act of 1971 provided the National Cancer Institute (NCI) with the impetus to create an era of molecular oncology and to discover, develop, and deliver a new generation of advanced biomedical technologies. With gene and protein microarrays, nanotechnology, information technologies, and advanced molecular imaging systems, preempting the process of cancer has become an achievable reality.

I am encouraged and excited by what our Nation's cancer program has accomplished and what each achievement means for the future, and I laud the work of our NCI scientists and the many researchers who we support through our various programs. I hope you enjoy reading this report, which describes a sample of our scientific and programmatic accomplishments in 2004. NCI's wide-ranging and diversified efforts are strategically focused to prevent, detect, eliminate, and control cancer, and collectively they serve to move us closer to eliminating cancer as a cause of suffering and death.

Andrew C. von Eschenbach
Director
National Cancer Institute

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Introduction

The National Cancer Institute's Annual Report for 2004, *The Nation's Progress in Cancer Research*, provides an overview of the breadth and depth of NCI-sponsored research that spans the seamless continuum of discovery, development, and delivery and includes new and effective interventions against the complex group of diseases called cancer. Keep in mind that the research presented here is just a sampling of the work being done by NCI scientists and our grantees. You will find fascinating and encouraging reports from the nation's—and the world's—laboratories, medical clinics, and patients' bedsides that show the progress being made toward NCI's Challenge Goal to eliminate the suffering and death due to cancer by 2015.



Discovery

Development

Delivery

Discovery

Discoveries are occurring at an increasing frequency, and they illuminate a path forward to render cancer a manageable disease that will no longer be a threat to life. For example, finding and characterizing cancer "susceptibility" genes are of vital importance to identify individuals at risk, as well as for use as potential targets for molecular intervention. In 2004, studies tracked an inherited lung cancer susceptibility gene to chromosome 6 and identified a known melanoma susceptibility gene that also increases the risk of pancreatic cancer. Another series of studies suggest that overexpression of *FUS1* tumor suppressor genes, which are lost or inactivated in the tumors of most lung cancer patients, can suppress tumor growth, even in patients with late-stage disease. Finally, the discovery of the *Twist* gene for metastasis provides new hope for controlling the spread of cancer.

Development

The development of these exciting discoveries into useful new interventions is also advancing at a brisk pace. In 2004, a new combination drug therapy called FOLFOX has already helped patients in clinical trials with previously untreated, metastatic colorectal cancer. Similarly, the drug bortezomib (Velcade®) has proven effective in trials for patients with multiple myeloma who have relapsed and become resistant to standard treatments.

Convergent with these advances is the emergence of new imaging technologies and nanotechnology that enable us to detect the development of cancer at the microscopic and molecular levels, such as by monitoring the erosion of telomeres (the ends of chromosomes) which is linked to the initiation of some tumors. Tracking these cellular processes makes possible the

identification of new biomarkers for cancer prevention, detection, and the monitoring of patients undergoing treatment, and it also allows for early intervention.

The advent of molecular medicine also addresses one of the more vexing questions facing cancer researchers: why do two patients with seemingly identical cancer types have two different responses to the same chemotherapy? We now know that genetics plays a major role in this responsive/unresponsive phenomenon. Featured in this report is a study in which researchers, using gene profiling technology, identified a gene expression pattern for primary mediastinal B-cell lymphoma that distinguishes it from other types of large B-cell lymphomas with poorer response rates to chemotherapy. Understanding these subtle genetic differences provides us with the opportunity to identify potential patient responders to various treatments and to develop and pursue other strategies for those who are not likely to respond.

Delivery

NCI works diligently with other government health care agencies, medical institutions, patient advocacy groups, and many other partners to ensure that the latest advances in cancer prevention, diagnosis, and treatment are delivered to all individuals who can benefit from them. For example, NCI's Cancer Information Service (CIS) and the Centers for Disease Control and Prevention (CDC) have been working on the front lines of delivery by implementing a national network of tobacco cessation telephone "quitlines" to bring resources within reach of all people in the United States who wish to stop smoking. NCI also strengthened its ongoing commitment to preventing and eliminating health disparities in 2004 through a partnership with African American churches to improve the nutritional habits of their congregations. In addition, NCI's new Cancer Disparities Research Partnership Program expanded its effort to assist community clinics in underserved areas by partnering them with NCI-designated Comprehensive Cancer Centers, helping the clinics to provide better oncology care and enabling their patients to participate in clinical trials of promising new agents.

Organization of This Report

Our Annual Report begins with a section called *In Focus* that highlights several scientific advances that illustrate NCI's focus on the areas of discovery, development, and delivery. These are followed by descriptions of other scientific and programmatic advances that are grouped into sections based on the eight strategic areas identified by NCI leadership as essential for reaching our Challenge Goal to the nation:

1. Understand the Causes and Mechanisms of Cancer
2. Accelerate Progress in Cancer Prevention
3. Improve Early Detection and Diagnosis
4. Develop Effective and Efficient Treatments
5. Understand the Factors that Influence Cancer Outcomes
6. Improve the Quality of Cancer Care
7. Improve the Quality of Life for Cancer Patients, Survivors, and Their Families
8. Overcome Cancer Health Disparities

As this Annual Report indicates, NCI is committed to an integrated approach to marshalling all of the many resources and approaches necessary to make cancer a condition that is—at worst—a manageable, chronic illness similar to most cases of heart disease and diabetes. This report highlights profiles on groundbreaking research—examples of NCI's concerted, systematic approach to reaching this goal.

NCI supports cancer research across an integrated continuum of discovery, development, and delivery. Our aim is to make this research as seamless as possible. NCI's activities across this continuum are broad—encompassing basic biology, epidemiology, behavioral research, and other disciplines. This "In Focus" section highlights a sample of the broad spectrum of research undertaken in 2004 in these three important areas.

In Focus: Discovery, Development, and Delivery

Discovery

Discovery research unveils and explores the mechanisms that underlie the inner workings of cancer cells, identifies potential weak points in cancer-causing pathways that may be vulnerable to molecularly-targeted therapy, and screens millions of compounds for candidate cancer drugs. NCI-supported researchers pinpoint cancer-causing genetic mutations in cancer-prone families, identify environmental factors and behaviors that may increase cancer risk, reveal the causes of cancer health disparities, and much more. The following advances are good examples of the progress we made in discovery research in 2004.

Targeting the "Twist" Gene May Be One Key to Halting the Spread of Cancer

NCI-supported researchers have identified a gene—called *Twist*—that may act as a "master switch" allowing cancer cells to spread, or metastasize. This discovery opens the door to further research that may lead to novel therapies targeting the *Twist* gene and aimed at reducing mortality from metastasis, the leading cause of cancer death.

Artwork of cancer cells breaking away from a tumor. Credit: Russell Kightley/Photo Researchers, Inc.

During the development of an embryo, the *Twist* gene plays an important role in cell movement and tissue formation. When the gene is active, embryonic cells are able to move to their proper location and differentiate into tissues and structures found in the adult. The *Twist* gene is not usually active in adults.

In many cancer cells, however, the *Twist* gene is again turned on, and the cells stop making a protein called E-cadherin that keeps them stuck together and anchored in their proper location. Without E-cadherin, cancer cells can become mobile and spread beyond their original tissue site.

Robert Weinberg, Ph.D., of the Whitehead Institute for Biomedical Research and the Massachusetts Institute of Technology—along with colleagues from Harvard Medical School, France, and Israel—analyzed four cell lines in a mouse model of breast cancer. Cells from each of these four lines form breast (mammary) tumors in mice, but differ in their ability to spread beyond mammary tissue.

The scientists reported that cells from the first line (called 67NR) do not spread outside the mammary gland to other locations in the body. Cells from the second line (168FARN) can spread to nearby lymph nodes, but not to the lungs or other organs. Cells from the third line (4TO7) sometimes spread to the lungs, but cannot form new tumors there. Lastly, cells from the most aggressive line (4T1) are able to metastasize and form tumors in the lungs.

Gene expression in the four cell lines was then compared using gene expression profiling, which identifies which genes are "turned on." The *Twist* gene was highly expressed in the three mouse cell lines that are able to spread; that was not the case, however, in the non-metastatic cell line 67NR. The *Twist* gene was also not expressed in normal mouse or human breast cells. Therefore, *Twist* appears to be overexpressed only in cells that are prone to metastasize.

When the researchers blocked *Twist* gene expression in cells from the aggressive cell line 4T1 and then injected the cells into mice, they found the cells could no longer spread to the lungs. The researchers also studied human breast cancer tissue, discovering that *Twist* was expressed at high levels only in very invasive tumor types.

Suresh Mohla, Ph.D., chief of the Tumor Biology and Metastasis Branch in NCI's Division of Cancer Biology, notes, "Together, the findings present a good picture that the activation of *Twist* and its associated cellular processes are important for tumor metastasis. A normal tumor may shed millions of cells a day, but very few can survive and take up residence elsewhere. These investigators showed that tumor cells are very clever and are able to overcome these barriers by appropriating the function of a very latent protein. That helps them move in and out of blood vessels and into tissues, form new colonies, and grow."

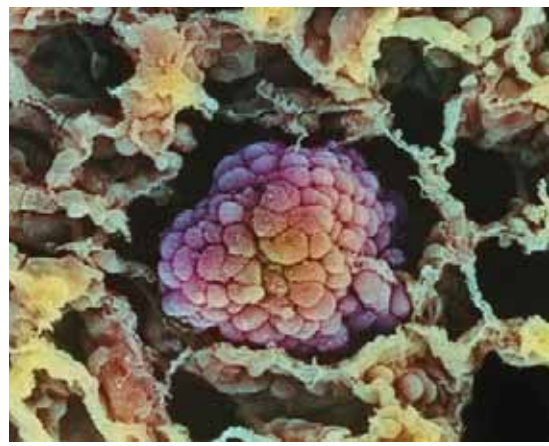
Research into how *Twist* functions in metastasis is still preliminary and must be confirmed in other studies, including human studies. Nonetheless, NCI scientists believe the available evidence points to potential diagnostic and treatment applications through the suppression of *Twist* gene activity. This research may also help clinicians to identify more aggressive cancers that pose a higher risk for metastasis. NCI is supporting research into other factors

and genes that may contribute to metastasis, such as the *TrkB* gene that allows cancer cells to survive after they have detached from a tumor. Investigators are also looking at the *Rho* gene, which appears to prevent new cancer cells from adhering to the tumor.

Yang J, Mani S, Donaher J, Ramaswamy S, Itzykson R, Come C, Savagner P, Gitelman I, Richardson A, Weinberg R. *Twist*, a master regulator of morphogenesis, plays an essential role in tumor metastasis. *Cell*, June 25, 2004; 117(7):927-939.

Replenishing Deleted Gene Holds Promise for Lung Cancer

Scientists at the M.D. Anderson Cancer Center and the University of Texas Southwestern Medical Center have reported encouraging early results in studies of a human tumor suppressor gene—called *FUS1*—and its protein product that one day may prove useful for the prevention, early detection, and treatment of lung cancer.



Colored scanning electron micrograph (SEM) of a small cancerous tumor filling an alveolus of the lung. Credit: Moredun Scientific/Photo Researchers, Inc.

At least one copy of the *FUS1* gene is deleted in 80 percent of lung cancers. *FUS1* is also frequently deleted in pre-invasive lesions of the lung. The protein product of the *FUS1* gene is normally modified after it is made by the addition of a type of fat molecule called myristic acid. This modification helps direct the *FUS1* protein to its proper location in the cell. When the modification doesn't take place, the unmodified protein is destroyed by the cell.

In lung cells missing one copy of the *FUS1* gene, deletion or mutation of the remaining copy—or not adding myristic acid to its protein product—leads to a loss of *FUS1* tumor suppressor activity and the development of lung cancer.

When the scientists encased *FUS1* DNA in microscopic particles of fat called liposomes and injected the particles into human lung cancers growing in mice, the tumor cells that made *FUS1* protein either stopped growing or were destroyed. Furthermore, when *FUS1* DNA-containing liposomes were injected into the bloodstream of mice that had developed metastatic human lung tumors, the number of metastatic tumors was reduced, and the mice lived significantly longer than control mice (an average of 80 days compared with an average of 48 days).

Based on these results, a phase I clinical trial is under way to see if liposome-encapsulated *FUS1* DNA can inhibit tumor growth in patients with late-stage lung cancer. Early results show that lung tumors in five out of six treated patients have stopped growing and remain stable more than a year after treatment. The liposomes are not toxic to humans.

"The delivery of liposome-encapsulated *FUS1* DNA into the bloodstream potentially represents a new form of lung cancer therapy," says Jack Roth, M.D., lead investigator of the *FUS1* studies and leader of the University of Texas SPORE (Specialized Programs of Research Excellence) in Lung Cancer. John Minna, M.D., another investigator in this study, added, "We would also like to determine whether *FUS1* liposomes can be given as an aerosol to prevent the development of lung cancer in people whose lungs have been damaged by smoking."

Uno F, Sasaki J, Nishizaki M, Carboni G, Xu K, Atkinson E, Kondo M, Minna J, Roth J, Ji L. Myristoylation of the *FUS1* protein is required for tumor suppression in human lung cancer cells. *Cancer Research*, May 1, 2004; 64(9):2969-2976.

Ito I, Ji L, Tanaka F, Saito Y, Gopalan B, Branch C, Xu K, Atkinson E, Bekele B, Stephens L, Minna J, Roth J, Ramesh R. Liposomal vector mediated delivery of the 3p *FUS1* gene demonstrates potent antitumor activity against human lung cancer *in vivo*. *Cancer Gene Therapy*, November 2004; 11(11):733-739.

Development

Development research moves promising new scientific discoveries in cancer research to the next stage—the development of evidence-based interventions that can improve cancer care. In preclinical investigations, scientists test promising cancer drug candidates, early detection and treatment-monitoring technologies, and other potential interventions for sensitivity, specificity, reproducibility, and accuracy. Interventions that pass this scrutiny advance to phase I clinical trials in humans for safety and preliminary effectiveness testing. Later-stage clinical trials evaluate experimental interventions in larger groups of people. Equally important is NCI-supported development of discoveries in the fields of cancer epidemiology, cancer communications, quality of care, health disparities, and cancer surveillance. The following examples illustrate the scientific advances made in development research in 2004.

New Combination Therapy Prolongs Survival for Patients with Metastatic Colon Cancer

Patients with previously untreated metastatic colorectal cancer survived significantly longer, had longer intervals without tumor progression, and experienced fewer side effects than those receiving standard therapy in a randomized, clinical trial that tested a new combination drug regimen developed by several NCI-supported research groups. The new regimen, known as FOLFOX, combines two existing cancer drugs (5-fluorouracil and leucovorin) with a new drug oxaliplatin (Eloxatin).

In 2004, close to 150,000 people were diagnosed with colorectal cancer in the United States and approximately 57,000 died from the disease. About 10 percent of United States cancer deaths each year are due to colorectal cancer. The 5-year survival rate for localized cancer is 90 percent, but survival drops to 9 percent when the disease is diagnosed at an advanced stage.

The clinical trial of FOLFOX involved 795 participants. Each patient was randomly assigned to one of three chemotherapy combinations—the standard therapy of irinotecan, 5-fluorouracil, and leucovorin (IFL); irinotecan and oxaliplatin (IROX); or FOLFOX. Patients treated with FOLFOX survived 30 percent longer than those treated with IFL (median survival was 19.5 months for FOLFOX versus 15 months for IFL). FOLFOX-treated patients also survived significantly longer without signs of tumor progression (median time to tumor progression was 8.7 months for FOLFOX versus 6.9 months and 6.5 months for IFL and IROX, respectively). Patients who received FOLFOX also had a higher response rate than those who received the other treatment regimens. Overall, the side effects of FOLFOX were generally less severe and more manageable than the effects observed with the other two drug combinations.

"The results of this study were the main evidence used by the FDA to approve FOLFOX for the indication of treatment of previously untreated patients with advanced colorectal cancer," says Richard Goldberg, M.D., of the University of North Carolina at Chapel Hill, principal investigator of the FOLFOX trial. "The study was also responsible for a shift in the prescribing patterns of oncologists in the United States to an oxaliplatin-based regimen as their first line of chemotherapy in this patient group."

Goldberg R, Sargent D, Morton R, Fuchs C, Ramanathan R, Williamson S, Findlay B, Pitot H, Alberts S. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *Journal of Clinical Oncology*, January 1, 2004; 22(1):23-30.

New Treatment Found for Drug-Resistant Multiple Myeloma

The drug bortezomib (Velcade®)—one of a new class of drugs called proteasome inhibitors—has proven effective in clinical trials for patients with multiple myeloma that has relapsed and become resistant to standard treatments.

In a phase III trial, 669 patients with relapsed multiple myeloma were randomly assigned to receive bortezomib or high-dose dexamethasone, an agent commonly used to treat multiple myeloma. Those receiving bortezomib had higher response rates, a longer time to disease progression, and greater survival times.

Bortezomib works by inhibiting the activity of structures inside cells called proteasomes. Proteasomes are like garbage disposals that chew up abnormal or damaged proteins so they can not interfere with the normal workings of the cell. By blocking this garbage disposal system, bortezomib allows proteins to build up in myeloma cells and forces the cells into apoptosis—"suicide mode."

"Bortezomib represents a new paradigm in myeloma treatment because it targets both the tumor cell and bone marrow microenvironment to overcome resistance to conventional therapies," says Kenneth C. Anderson, M.D., of Boston's Dana-Farber Cancer Institute. Anderson is the senior author of the published report of the phase III trial. He is also the principal investigator of the NCI-supported Myeloma SPORE (Specialized Programs of Research Excellence).

Anderson and his colleagues are using gene profiling, proteomics, cell-signaling studies, and animal models to define the drug's exact mechanisms of action. These kinds of correlative studies are helping them devise new clinical trials to couple bortezomib with therapies that may enhance its activity and prevent the emergence of resistance to the new therapy.

Bortezomib received accelerated approval by the Food and Drug Administration in 2003 for patients with drug-resistant multiple myeloma. NCI is sponsoring more than 30 clinical trials with bortezomib—alone or in combination with other treatments—in lymphoma,

myeloma, leukemia, and cancers of the liver, colon and rectum, head and neck, lung, stomach, esophagus, kidneys, bladder, and ovaries.

Richardson P, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, Rajkumar S, Srkalovic G, Alsina M, Alexanian R, Siegel D, Orlowski R, Kuter D, Limentani S, Lee S, Hideshima T, Esseltine D, Kauffman M, Adams J, Schenkein D, Anderson K. A phase 2 study of bortezomib in relapsed, refractory myeloma. *New England Journal of Medicine*, June 26, 2003; 348(26):2609-2617.

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Richardson P, Sonneveld P, Schuster M, Irwin D, Stadtmauer E, Facon T, Harousseau J, Ben-Yehuda D, Lonial S, Goldschmidt H, Reece D, San-Miguel J, Blade J, Boccadoro M, Cavenagh J, Dalton W, Boral A, Esseltine D, Porter J, Schenkein D, Anderson K. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *New England Journal of Medicine*, June 16, 2005; 352(24):2487-2498.

Delivery

Delivering interventions that emerge from discovery and development research is ultimately the responsibility of health care providers and public health agencies. Nonetheless, NCI uses a variety of mechanisms and forms diverse partnerships to ensure our research findings reach local communities and are translated into practices that will make a difference in peoples' lives. We proactively disseminate information about research findings, opportunities to participate in clinical trials, and new interventions through a range of cancer communications activities that supplement the efforts of medical journals and the news media. The following examples illustrate our progress towards fostering the delivery of new cancer interventions in 2004.

Network of Phone "Quitlines" Provides Assistance to Smokers Who Want to Quit

Tobacco use is the number one preventable cause of premature death in the United States. The use of tobacco products has been associated with cancers of the lung, oral cavity, nasal cavity, trachea, larynx, pharynx, esophagus, stomach, pancreas, liver, colon, kidney, bladder, and cervix, as well as with myeloid leukemia, other lung diseases, heart disease, and stroke. Currently, 46 million Americans smoke and 70 percent of those smokers would like to quit.

An Information Specialist from NCI's Cancer Information Service.

Studies have shown that telephone counseling services—known as tobacco or smoking "quitlines"—can be especially helpful for people who lack access to other smoking cessation resources. Quitlines can also be an effective adjunct to other methods people use to quit. Randomized trials have also shown that telephone counseling can significantly increase long-term quit rates when compared to the use of self-help materials alone.

To provide the highest level of assistance to smokers across the country who want to quit, the U.S. Department of Health and Human Services (HHS) established a new toll-free telephone number (1-800-QUITNOW) in 2004 that serves as a single access point to an evolving national network of tobacco quitlines operated by many states. By providing one easy-to-remember telephone number, smokers in every state will have access to support services and the most up-to-date information they need to quit.

"The benefit of this network is that it provides a single access point for smokers so that every smoker can get the tools that he or she needs to stop smoking," said former HHS Secretary Tommy G. Thompson when he announced the launch of the national network of quitlines.

This initiative is being implemented by NCI's Cancer Information Service (CIS), the Centers for Disease Control and Prevention (CDC), and the North American Quitline Consortium.

The initiative has three main components:

- States with existing quitlines will receive increased funding to enhance their existing quitline services. Currently, 36 states have tobacco quitlines that deliver information, advice, support, and referrals to smokers, regardless of their geographic location, race, ethnicity, or economic status. States can use the additional funding to expand their quitlines' hours of operation, hire bilingual counselors, build referral links to local health care systems, or promote quitlines to more individuals.

- States that do not have quitlines will receive grants to establish them and to provide their residents with the tools they need to quit smoking.

- NCI CIS telephone counselors will provide assistance to individuals in states that do not have quitlines.

The CIS will continue to offer smoking cessation counseling in English and in Spanish through NCI's Smoking Quitline (1-877-44U-QUIT) and in English through the NCI Web site's LiveHelp Service (https://cissecure.nci.nih.gov/livehelp/welcome.asp). In addition, the NCI and HHS are exploring partnerships with quitlines that currently provide additional language services to help meet the needs of smokers who do not speak English or Spanish. Finally, an Internet-based service—www.smokefree.gov—is now available and provides access to quitline numbers currently offered by individual states and the NCI. The smokefree.gov site also offers an online guide to quitting, instant messaging with NCI experts on smoking cessation, and downloadable guides on how to stop using tobacco products.

1-800-QUITNOW

1-877-44U-QUIT

https://cissecure.nci.nih.gov/livehelp/welcome.asp

www.smokefree.gov

Molecular Test Predicts Risk of Breast Cancer Recurrence for Many Women

Researchers have developed a molecular test that helps to determine the risk of distant recurrence—that is, recurrence outside the breast—for women who have been treated for early stage, estrogen-dependent breast cancer. This information can help a woman and her doctor decide whether or not she should receive chemotherapy in addition to standard hormonal therapy with the drug tamoxifen or an aromatase inhibitor.

The test, called onco*type* DX™, is used to predict the 10-year risk of distant breast cancer recurrence. It is now offered as a reference test by an approved lab and can be used with nearly 50 percent of all newly diagnosed breast cancer patients in the United States. Recent research studies suggest that women with high recurrence scores on onco*type* DX™ testing will benefit from chemotherapy, whereas the benefit for women with low recurrence scores would be negligible.

To use the onco*type* DX™ test, the breast tumor and surrounding tissue are removed during surgery and sent to a pathology laboratory where the tissue specimen is preserved, or fixed, by being embedded in paraffin wax. Ribonucleic acid (RNA) is extracted from several thin sections of the specimen and used to analyze the expression levels of 21 genes in the tumor. The results of this gene expression analysis are then converted into a recurrence score from 0 to 100. A score of 17 or less indicates a low risk of distant recurrence. A score of 18 to 30 indicates an intermediate risk of distant recurrence, and a score of 31 or higher indicates a high risk of distant recurrence.

The onco*type* DX™ test was developed through collaboration of the National Surgical Adjuvant Breast and Bowel Project (NSABP), a clinical trials cooperative group supported by the NCI, and Genomic Health, Inc.

"This test has the potential to change medical practice by sparing thousands of women each year—for whom disease recurrence is unlikely—from the unnecessary and harmful side effects associated with chemotherapy," says JoAnn Zujewski, M.D., senior investigator in NCI's Cancer Therapy Evaluation Program.

Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner F, Walker M, Watson D, Park T, Hiller W, Fisher E, Wickerham D, Bryant J, Wolmark N. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *New England Journal of Medicine*, December 30 2004; 351(27):2817-2826.

Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner R, Walker M, Watson D, Bryant J, Wolmark N. Risk classification of breast cancer patients by the Recurrence Score assay: comparison to guidelines based on patient age, tumor size, and tumor grade. *27th Annual San Antonio Breast Cancer Symposium*, 2004.

Cancer is a complex set of diseases that scientists are striving to understand from multiple perspectives. Research that improves our understanding of its causes and the mechanisms that underlie its development—from assessing cancer risk to explaining the process of metastasis—is essential to our ability to develop and apply interventions to preempt cancer initiation and progression. NCI supports individual efforts as well as large interdisciplinary and multidisciplinary programs to unravel the complexities of multiple cancer risk factors and to understand specific types of cancer. This research forms the foundation for effective interventions to prevent, detect, diagnose, and treat cancer and to predict patient response to therapy. The advances described in this section provide a glimpse of the progress NCI has made in 2004 towards understanding the causes and mechanisms of cancer.

1

Understanding the Causes and Mechanisms of Cancer

Inherited Lung Cancer Gene Tracked to Chromosome 6

Scientists have pinpointed the approximate genetic address that appears to be associated with inherited lung cancer risk. The researchers with the Genetic Epidemiology of Lung Cancer Consortium—a collaboration of 12 universities and research institutions, including the National Human Genome Research Institute—looked at 52 families in which at least three first-degree family members had been diagnosed with lung, laryngeal, or throat cancers. Using genetic markers—DNA sequences at known locations on human chromosomes—the scientists identified a region on chromosome 6 as the probable neighborhood of the offending gene.

Jonathan Wiest

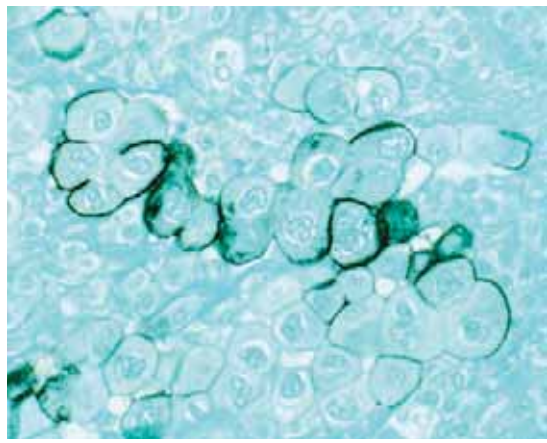
Exactly which gene is the culprit remains unknown at this time, notes Jonathan Wiest, Ph.D., with NCI's Center for Cancer Research. He likens the genetic markers used to identify the lung cancer susceptibility gene's location to mile markers on a highway. "The markers don't tell you what is located nearby—just where you are along the chromosome," Wiest says.

Identifying the specific gene from among numerous likely candidates will take at least two years of looking more closely at chromosome 6, Wiest predicts. Such a discovery may make possible genetic screening to identify those individuals at higher risk of lung cancer based on an inherited factor. The identified individuals could then be followed closely for early detection and treatment.

In an important related finding from the study, any amount of smoking—even a small amount—seemed to increase the risk of lung cancer substantially among carriers of the suspected gene. For non-carriers, on the other hand, the risk increased proportionately the more they smoked.

Bailey-Wilson J, Amos C, Pinney S, Petersen G, de Andrade M, Wiest J, Fain P, Schwartz A, You M, Franklin W, Klein C, Gazdar A, Rothschild H, Mandal D, Coons T, Slusser J, Lee J, Gaba C, Kupert E, Perez A, Zhou X, Zeng D, Liu Q, Zhang Q, Seminara D, Minna J, Anderson M. A major lung cancer susceptibility locus maps to chromosome 6q23-25. *American Journal of Human Genetics*, September 2004; 75(3):460-474.

Melanoma Susceptibility Gene Also Increases Risk of Pancreatic Cancer



Human tumor cells from the pancreas.

A gene mutation known to increase a person's risk of developing melanoma may also make individuals with this mutation more prone to developing pancreatic cancer, according to a study by scientists in NCI's Division of Cancer Epidemiology and Genetics (DCEG).

The NCI researchers examined the incidence of non-melanoma cancers among 253 people from 15 families with a history of melanoma and in which mutations in the *CDKN2A* gene, a known melanoma susceptibility gene, had been identified. They compared cancer incidence among 117 family members who tested positive for a mutation (carriers) and 136 who tested negative (noncarriers). These individuals were followed prospectively for 4 to 26 years starting in the 1970s.

Family members who had a *CDKN2A* mutation were found to be at significantly increased risk of developing any type of non-melanoma cancer, although the risk was limited mainly to digestive system tumors, particularly pancreatic cancer. Twelve of the mutation carriers developed a non-melanoma cancer during the study's observation period, compared with only two of the noncarriers. Pancreatic cancer was diagnosed in four of the mutation carriers and in none of the noncarriers. The number of pancreatic cancers expected to develop in the mutation carriers was 0.1, based on the incidence of pancreatic cancer in the general population.

Alisa Goldstein

The association between *CDKN2A* gene mutation and the susceptibility to various cancers had been suggested by earlier studies, including a review by DCEG's Alisa Goldstein, Ph.D.—lead investigator of this study—who analyzed published reports of pancreatic cancer in melanoma-prone families. However, unlike most of the earlier studies, the *CDKN2A*-mutation status of all participants in this study was individually determined.

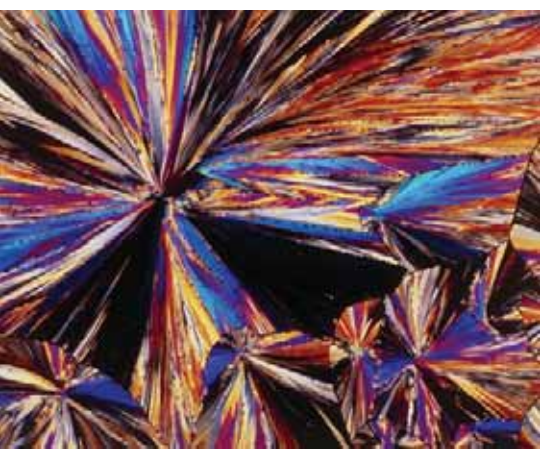
Despite the increased non-melanoma cancer risk associated with *CDKN2A* gene mutations in this study, melanoma remained the most common cancer developed by mutation carriers.

As in the general population, individuals at high risk for melanoma can reduce their risk by reducing sun exposure and monitoring their skin for early warning signs.

With regard to the *CDKN2A* gene's suggested association with pancreatic cancer, Goldstein cautions that additional analysis is required because of the limited sample size and the narrow spectrum of *CDKN2A* mutations in the studies undertaken thus far. "In the next five years, we hope to clarify the relationship between melanoma, pancreatic cancer, and *CDKN2A* gene mutations," says the NCI investigator. "We believe ongoing studies will be very important in furthering our understanding of the etiology of pancreatic cancer, which currently is poorly understood."

Goldstein A, Struewing J, Fraser M, Smith M, Tucker M. Prospective risk of cancer in CDKN2A germline mutation carriers.*Journal of Medical Genetics*, June 2004; 41(6):421-424.

Goldstein A. Familial melanoma, pancreatic cancer and germline CDKN2A mutations. *Human Mutation*, May 5, 2004; 23(6):630.



Polarized light micrograph of crystals of an androgen. Credit: Sidney Moulds/Photo Researchers, Inc.

New Insights into Hormone-Independent Prostate Cancer Offer Hope for Better Treatments

The most common type of prostate cancer is called "hormone-dependent." It is often treated by lowering blood levels of the male hormone testosterone in combination with treatments that target the hormone receptors in prostate cancer cells. These treatments are initially effective but ultimately fail because the growth of prostate cancer cells eventually becomes "hormone-independent." Research results from two groups of investigators have now provided new insights into why this happens and suggests ways it might be avoided.

When prostate cancer is first diagnosed as being hormone-dependent, it means that the tumor needs androgens (male hormones) to grow. Androgens bind to a protein called the androgen receptor inside prostate cancer cells, and the resulting hormone-receptor complex turns on cellular machinery that drives tumor growth.

One group studying the hormone-independence problem was led by Charles L. Sawyers, M.D., of the Howard Hughes Medical Institute, David Geffen School of Medicine, Jonsson Comprehensive Cancer Center, University of California at Los Angeles (UCLA).

Using gene expression profiling and other state-of-the art methods, Sawyers' group discovered that androgen receptor levels are higher in prostate cancer cells that have become hormone

independent. They also found that elevating androgen receptor levels in hormone-dependent prostate cancer cells by only three-fold was sufficient to make the cancer cells become hormone independent. These higher levels of androgen receptors enable prostate cancer cells to grow in the presence of very small amounts of androgen. Furthermore, the investigators discovered that, when androgen receptor levels are elevated, the prostate cancer drug bicalutamide (Casodex®)—which competes with androgens for binding to the androgen receptor and, therefore, blocks the effects of androgens in the prostate—acted like an androgen instead of an antiandrogen, and thus promoted tumor cell growth as well.

"Androgen receptor overexpression is one way a prostate tumor is able to escape therapy," Sawyers says. "It is critical to the tumor's survival." The UCLA team is doing additional research to determine how androgen receptors are able to use antiandrogens, such as bicalutamide, as androgens. They hope to identify a new generation of antiandrogen treatments that prostate cancer cells cannot hijack in this way.

The other research team, which was led by James L. Mohler, M.D., of the Roswell Park Cancer Institute, discovered that patients who developed hormone-independent, recurrent prostate cancer while undergoing treatment aimed at reducing androgen levels in their bodies had enough androgen in their tumor tissue to activate the androgen receptor. Whether these androgens were made by the adrenal gland or the tumor tissue itself is not clear.

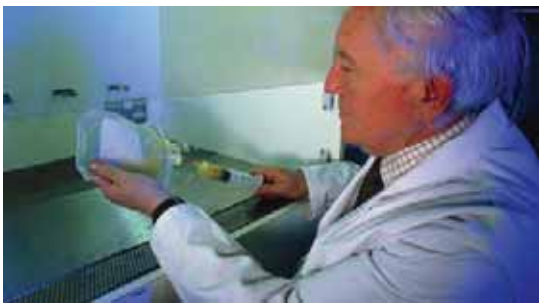
Taken together, these two sets of results indicate that hormone-independent prostate cancer is not really hormone independent after all. Both research groups see opportunities in these results for the development of more effective treatments for advanced prostate cancer.

Chen C, Welsbie D, Tran C, Baek S, Chen R, Vessella R, Rosenfeld M, Sawyers C. Molecular determinants of resistance to antiandrogen therapy. *Nature Medicine*, January 2004; 10(1):33-39.

Mohler J, Gregory C, Ford O 3rd, Kim D, Weaver C, Petrusz P, Wilson E, French F. The androgen axis in recurrent prostate cancer. *Clinical Cancer Research*, January 2004; 10(2):440-448.

Treatment for Bone Marrow Disorder Increases Risk of Cancer

Treatments for cancer or other diseases may sometimes increase a patient's risk for developing and dying from cancer later in life. Scientists at NCI and the Hôpital Saint Louis in Paris, France have discovered this is especially the case for patients with Fanconi anemia (FA), an inherited disease that primarily affects the bone marrow.



Preparing white blood cells from donated bone marrow for transplant. Credit: Simon Fraser/Photo Researchers, Inc.

Patients with FA suffer from a decreased production of all types of blood cells—a condition called aplastic anemia—which leads to other problems, such as infections, bleeding, and fatigue. These patients also have a high risk of leukemia and certain kinds of solid tumors. The only current long-term treatment for FA is bone marrow transplantation. While this procedure normally has risks, the risks appear to be compounded in FA patients.

In a study involving 262 individuals, the researchers demonstrated that bone marrow transplantation increases the already elevated risk of squamous cell cancer, primarily of the head and neck, in patients with FA. Patients who underwent bone marrow transplantation had a 4.4-fold higher risk of developing squamous cell cancer than those who did not undergo this procedure. Furthermore, the cancers occurred at significantly younger ages among the transplant patients, with a median age of onset of 18 years among transplant patients compared with a median age of onset of 33 years for patients who had not undergone transplantation.

Blanche Alter

"Our data suggest that clinicians should advise FA patients about long-term complications, including squamous cell cancers of the head and neck," says Blanche P. Alter, M.D., M.P.H., of NCI's Division of Cancer Epidemiology and Genetics and one of the two NCI authors of the study's report. "Long-term surveillance for cancer should start soon after transplant, even in young recipients," she cautions.

Alter is leading a prospective cohort study of persons with FA and other inherited bone marrow-failure syndromes to provide specific information about the types of cancer that develop in these patients and other associated risk factors, including complications from the transplants.

Rosenberg P, Socie G, Alter B, Gluckman E. Risk of head and neck squamous cell cancer and death in patients with Fanconi Anemia who did and did not receive transplants. *Blood*, January 1, 2005; 105(1):67-73.

Etiologic investigation of cancer susceptibility in Inherited Bone Marrow Failure Syndromes (IBMFS) http://marrowfailure.cancer.gov.

Ultraviolet B Rays in Sunlight Identified as Primary Risk Factor for Melanoma

Exposure to the ultraviolet (UV) rays in sunlight has long been recognized as a major risk factor for melanoma skin cancer, but it was not known whether longer UV wavelengths (UVA), shorter UV wavelengths (UVB), or both are the culprit. NCI-supported research now implicates UVB as the primary offender and shows that UVB exposure in combination with increased production of growth factors for melanocytes—the cells that give rise to melanomas—causes melanoma skin cancers in animal models of the human disease.

In one study that was reported in 2004, researchers at the George Washington University Medical Center (GWUMC) and at NCI irradiated newborn mice with a specialized light source that is able to produce UVA alone, UVB alone, a combination of UVA and UVB, or a simulation of regular sunlight. The mice were genetically engineered to over-produce a protein called hepatocyte (liver cell) growth factor/scatter factor (HGF/SF). HGF/SF had previously been shown to stimulate the growth, development, and motility (ability to move or migrate) of melanocytes. When they are exposed to UV light, these genetically-altered mice develop melanomas that are biologically similar to human melanomas. It is also of interest that only newborn mice of this type develop melanoma tumors when they are exposed to UV light. Mice irradiated as adults do not form melanomas in response to UV exposure. The researchers found that UVB rays, but not UVA rays, were able to induce melanomas in these high-risk mice.

In another study reported in 2004, researchers at the Wistar Institute, the Karolinska Institute, and the University of Pennsylvania grafted human skin from newborns and adults onto mice and then injected the grafts with DNA that contained the genetic instructions for three different human growth factors—basic fibroblast growth factor (bFGF), stem cell factor (SCF), and endothelin-3 (ET-3)—that had previously been shown to be growth factors for melanocytes. In skin grafts that overexpressed all three growth factors, melanomas could be induced by exposure to lamps containing a mixture of wavelengths including UVB. The tumors that developed in skin grafts from adults were less severe than those induced in skin grafts from newborns.

These findings are consistent with other evidence that suggests sunlight-induced skin damage during childhood has a greater influence on later melanoma development than sun-induced

skin damage during adulthood. Researchers plan to investigate this relationship further and to identify which UVB wavelengths pose the greatest risks for melanoma.

"By identifying UVB as the initiating waveband for melanoma, we are in a strong position to study narrow-band, wavelength-specific induction of melanoma throughout the UVB spectrum," says Edward C. De Fabo, Ph.D., research professor at GWUMC and lead investigator for the GWUMC and NCI study. "If successful, we will have developed a 'weighting' function that will allow us to measure melanoma-specific UVB doses from a given light source—be it the sun or artificial sources such as tanning lamps. This research could also lead to the development of more effective sunscreens and UVB monitoring and alerting systems," adds De Fabo.

De Fabo E, Noonan F, Fears T, Merlino G. Ultraviolet B but not ultraviolet A radiation initiates melanoma. *Cancer Research*, September 15, 2004;64(18):6372-6376.

Berking C, Takemoto R, Satyamoorthy K, Shirakawa T, Eskandarpour M, Hansson J, VanBelle P, Elder D, Herlyn M. Induction of melanoma phenotypes in human skin by growth factors and ultraviolet B. *Cancer Research*, February 1, 2004;64(3):807-811.

Collaborative Studies Cast a Wide Net to Understand the Causes of Cancer

One of NCI's top priorities is to understand how genes that increase an individual's susceptibility to cancer are influenced by environmental factors, such as a person's diet, the medications they take, or their exposures to chemicals.

To accomplish this goal, NCI fosters the development of research consortia—groups of collaborating institutions and investigators—to conduct both cohort and case-control studies of the interactions between genes and the environment that might contribute to the development of cancer. The creation of such consortia is part of the revolutionary shift to "big science," where multidisciplinary teams of scientists pool their resources and expertise to conduct research on a much larger scale.

One such endeavor is the Consortium of Cohorts, an international collaboration bringing together intramural and extramural investigators responsible for 23 independently funded population cohorts with 1.2 million participants, thousands of whom have developed cancer or are likely to be diagnosed with cancer in the near future. Each cohort within the consortium supplies extensive information on known or suspected risk factors for cancer, as well as biospecimens that are collected before the diagnosis of cancer.

A current study involves 600,000 individuals and focuses on the risks of breast and prostate cancer associated with variations in hormone- and growth factor-related genes. Participating in this study are the following cohorts: the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; the Alpha-Tocopherol Beta-Carotene Prevention Study; the Physicians' Health Study I and II; the Nurses' Health Study; the Health Professionals Follow-up Study; the Harvard's Women's Health Study; the American Cancer Society's Cancer Prevention Study-II; the European Prospective Investigation into Cancer and Nutrition; and the Multiethnic Cohort.

Investigators responsible for population- or hospital-based case-control studies have established case-control consortia to study the less common or highly lethal cancers that cannot be easily evaluated in cohort studies. In one example, NCI-supported investigators—inside and outside the Institute—have joined forces in a coordinated series of case-control studies focused on non-Hodgkin lymphoma (NHL). The International Lymphoma Epidemiology Consortium—or InterLymph—is focused on identifying the reasons for the increasing incidence of NHL around the world. InterLymph represents a new generation of large-scale molecular epidemiologic studies that have been initiated in North America, Europe, and Australia. This consortium includes essentially all major ongoing epidemiologic studies of NHL and provides a good model for the study of less common malignancies.

NCI is also establishing family-based consortia to identify major hereditary susceptibility genes, determine how they affect cancer risk, and study how that risk is modified by other genetic and environmental factors.

http://epi.grants.cancer.gov/Consortia/cohort.html

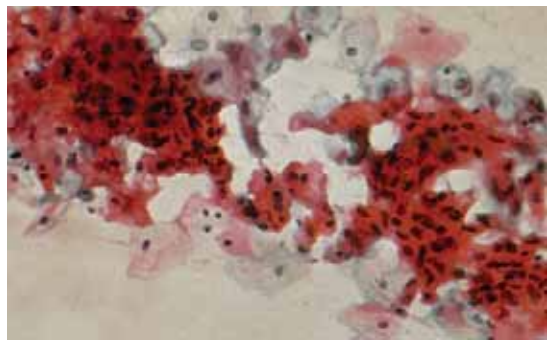
Prevention is our first line of defense against cancer. Efforts to prevent cancer focus on understanding and modifying behaviors that increase risk, mitigating the influence of genetic and environmental risk factors, and interrupting cancer-causing processes through early medical intervention. For example, discoveries made in 2004 about tobacco use and addiction are helping us to better understand how to prevent more people from starting to smoke and to equip smokers and other tobacco users with ways to quit. Our progress in chemoprevention research has brought us a step closer to a future where many cancers are preempted through use of well-tolerated medicines, vitamins and minerals, food components, and other agents. The following advances highlight some of this progress.

2

Accelerating Progress in Cancer Prevention

Vaccine Blocks Virus Infections Associated With Cervical Cancer

An experimental vaccine appears to provide nearly complete protection against infections caused by two strains of human papilloma virus (HPV) that are responsible for 70 percent of cervical cancers worldwide. In a randomized, controlled clinical trial, the vaccine was also found to be highly effective against persistent infections caused by the two strains—HPV-16 and HPV-18—as well as in preventing cellular abnormalities caused by these viruses.



Light micrograph of a cervical smear revealing infection with the human papilloma virus. Credit: Science Photo Library/ Photo Researchers, Inc.

The vaccine, produced by GlaxoSmithKline Biologicals, was based on technology developed by NCI scientists who were led by John Schiller, Ph.D., and Douglas Lowy, M.D., in NCI's Center for Cancer Research (CCR). Work done by Schiller, Lowy, and their CCR colleagues laid the foundation for the production of HPV "virus-like particle," or VLP, vaccines. VLPs contain the L1 outer coat protein of HPV and are noninfectious. They are produced in insect cells or yeast cells by use of recombinant DNA technology. The cells make large amounts of the L1 protein, which then self assembles into particles that look like HPV but do not contain the virus' genetic material.

The vaccine used in the clinical trial contained a mixture of HPV-16 and HPV-18 VLPs. In the trial, 1,113 women from Canada, Brazil, and the United States were randomly assigned to receive three doses of the HPV-16/18 vaccine or a placebo. The second and third doses of vaccine or placebo were given 1 month and 6 months after the initial injection. The researchers found that the vaccine was 91.6 percent effective in protecting against infections with HPV-16 or HPV-18 in women who were treated according to the trial's protocol. In addition, the vaccine was 100 percent effective in helping to eliminate virus infections that occurred during the study period, and it was 93.5 percent effective in preventing cervical cell abnormalities associated with HPV-16 or HPV-18 infection.

"The data from this study and others like it are extraordinarily strong," says NCI's Schiller. According to the scientist, HPV vaccination to prevent cervical cancer could have a substantial life-saving impact, especially in many developing countries that do not have screening to detect precancerous danger signs. Cervical cancer is the second-most common cancer among women worldwide and kills more than 200,000 women each year, most of them in developing countries.

Harper D, Franco E, Wheeler C, Ferris D, Jenkins D, Schuind A, Zahaf T, Innis B, Naud P, De Carvalho N, Roteli-Martins C, Teixeira J, Blatter M, Korn A, Quint W, Dubin G. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomized controlled trial. *Lancet*, November 13, 2004; 364(9447):1757-1765.

Heavy Smoking During Pregnancy Increases Risk of Lifetime Nicotine Dependence Among Offspring

New evidence provides the first link between maternal smoking during pregnancy and lifetime nicotine dependence among the mothers' offspring.

Raymond Niaura

Scientists from Brown and Harvard Universities interviewed 1,248 adult offspring of pregnant women who enrolled in the New England cohort of the National Collaborative Perinatal Project (NCPP) between 1959 and 1966. The NCPP was initially designed to collect information about the women's pregnancies and their children's development from the time the mothers enrolled in the study through the first seven years of their children's lives. The offspring were later contacted—when they were between 17 and 39 years of age—and interviewed about their history of nicotine and marijuana use and dependence.

The scientists found that the children of heavy smokers—defined as women who smoked a pack or more of cigarettes during any of their pregnancy days—were twice as likely to progress from ever smoking to nicotine dependence than the children of women who never smoked. The difference in progression to nicotine dependence remained the same between the two groups after adjusting for offspring gender and age at interview, as well as for their mothers' socioeconomic status and age at the time of pregnancy. The influence of maternal smoking on offspring appears limited to nicotine dependence and was not associated with marijuana dependence.

Credit: Ian Boddy/
Photo Researchers, Inc.

The link between maternal smoking during pregnancy and nicotine dependence in offspring is consistent with other evidence and suggests that fetal nicotine exposure affects the developing brain. Another explanation for these findings is that mothers who continued to smoke heavily after pregnancy exposed their children to high concentrations of nicotine in breast milk. A less likely explanation is that the children were exposed to nicotine in secondhand smoke.

The scientists noted that their findings have important public health implications. Nearly half of all women smokers in the United States

continue to smoke during their pregnancies—amounting to about 12 percent of all women who give birth in this country. This means that more than half a million infants annually are exposed to nicotine before they are born.

Buka S, Shenassa E, Niaura R. Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: a 30-year prospective study. *American Journal of Psychiatry*, November 2003; 160(11):1978-1984.

Major Prevention Trials Complete Recruitment of Study Participants

Two important, NCI-sponsored prevention trials completed large-scale recruitment of their study subjects in 2004—passing major milestones in the effort to determine whether certain dietary supplements, drugs, or other compounds can lower the risk of developing certain cancers.

The SELECT (Selenium and Vitamin E Cancer Prevention Trial) study is testing the effectiveness of the nutrients selenium and vitamin E in preventing prostate cancer. More than 35,000 men—age 55 and older—were recruited to participate in SELECT. Because prostate cancer generally strikes African American men more often and at an earlier age than Caucasian men, African Americans age 50 and older are also participating in the trial. Final results from SELECT are anticipated in 2013.

The STAR (Study of Tamoxifen and Raloxifene) trial is comparing the effectiveness of the drugs tamoxifen and raloxifene in preventing breast cancer in over 19,000 postmenopausal women who are at increased risk for the disease. Both drugs have been shown to reduce the risk of breast cancer in previous trials. The STAR trial is a head-to-head comparison of the two drugs. An important part of STAR is assessing the long-term safety of raloxifene versus tamoxifen in women at increased risk of breast cancer. Researchers hope to announce results from STAR sometime in 2006.

To foster research toward the discovery of new prevention agents, NCI's Division of Cancer Prevention (DCP) formed a multi-center Clinical Trials Consortium in 2003. This consortium is designed to encourage, support, and fund early-phase prevention trials. "We are seeking to identify agents or strategies that could later be tested and confirmed in a phase III trial," says Eva Szabo, M.D., chief of DCP's Lung and Upper Aerodigestive Cancer Research Group.

"The Consortium will test preliminary effectiveness of the next promising agents and also identify the appropriate population in which to conduct additional testing."

NCI works with six primary institutions and over 40 additional clinical sites that are part of the Clinical Trials Consortium. Among the Consortium's current studies are investigations into the use of an antidiabetic drug to reverse oral leukoplakia (abnormal patches of tissue in the mouth that may become cancerous); tea polyphenols to lower the risk for cancers of the cervix, breast, and esophagus; soy isoflavones to prevent bladder cancer; lycopene to prevent prostate cancer; and statins to reduce the risk of colorectal and melanoma skin cancers.

Agents that show promise in Consortium investigations will then be considered for larger trials, similar to SELECT and STAR.

http://www.cancer.gov/clinicaltrials/digestpage/SELECT

http://www.cancer.gov/clinicaltrials/digestpage/STAR

http://www.cancer.gov/newscenter/pressreleases/preventtrials

Large Study Links Obesity to Cancer Risks in U.S. Men

In one of the largest studies to investigate the relationship between obesity and cancer risks among men, NCI's Division of Cancer Epidemiology and Genetics (DCEG) has confirmed earlier associations between obesity and certain cancers—for example, colon, prostate, and kidney cancers—and identified possible associations between obesity and other types of cancer. The study also contributed important new information about obesity and cancer risks among African American men. Previous studies of the relationship between obesity and cancer were conducted primarily in American or European Caucasian populations.

The men (3,668,486 Caucasian and 832,214 African American) were military veterans who had been hospitalized in Veterans Administration hospitals with a diagnosis of obesity between 1969 and 1996. The men's health status was followed from the time they were discharged from the hospital until they were diagnosed with cancer, they died, or the follow-up period ended, whichever happened first. The incidence of cancer among men hospitalized with a diagnosis of obesity was compared with the incidence of cancer among men who had been hospitalized for other reasons.

The researchers found that, among Caucasian men, obesity significantly elevated the risk of cancers of the lower esophagus, gastric cardia (upper part of the stomach), small intestine, colon, rectum, liver, gallbladder, pancreas, ampulla of Vater (where ducts from the liver and pancreas enter the small intestine), breast, prostate, bladder, kidney, thyroid, and connective tissue, as well as of melanoma, multiple myeloma, and leukemia. These risks persisted for liver and pancreatic cancer even among the men who had no history of alcoholism or diabetes. Among African American men, obesity significantly elevated the risk of cancers of the colon, extrahepatic (outside the liver) bile ducts, prostate, kidney, and thyroid, as well as of melanoma, multiple myeloma, and leukemia.

"Although there were some differences, the incidence pattern for various types of cancer was generally similar for African American men and Caucasian men," says DCEG epidemiologist Claudine Samanic, M.A., M.S. "Since the rates of overweight and obesity are increasing in the United States as well as globally, we need to learn as much as we can about the relationship between excess body weight and cancer."

"As in every study, there are limitations with this study that require caution in interpreting the results, especially for the less common cancers," Samanic adds. "Researchers are trying to understand the ways in which obesity affects different cellular and hormonal processes in the body. We hope that exploring these and other mechanisms in more and more types of cancer will lead to better methods of treatment as well as prevention. In the meantime, these findings give us one more piece of evidence that fighting obesity must be a critical public health priority."

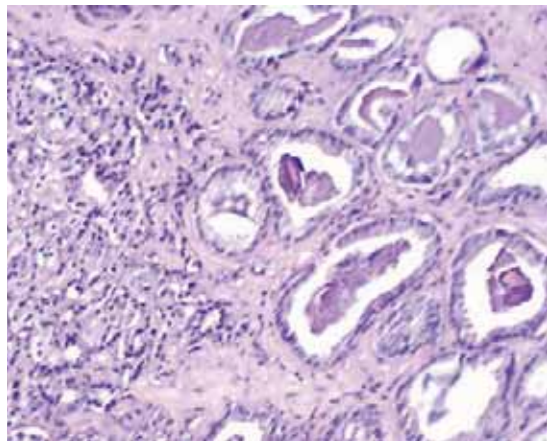
Samanic C, Gridley G, Chow W, Lubin J, Hoover R, Fraumeni J, Jr. Obesity and cancer risk among white and black United States veterans. *Cancer Causes and Control*, February 2004; 15(1):35-43.

Detecting and diagnosing tumors early in the disease process offer the best chance to treat tumors before they become invasive and metastatic. This can dramatically improve the odds of survival and eliminate many deaths. NCI-supported research enhances our understanding of existing screening technologies and how to maximize their effectiveness. We continue to develop cancer detection tests that use advanced technologies, such as gene expression profiling and proteomics, which can identify cancer in its earliest stages. New uses of imaging technology are improving the accuracy of cancer detection and providing valuable diagnostic information to help physicians develop the best treatment plan for individual patients. Below are some of the 2004 scientific advances in early detection and diagnosis research.

3

Improving Early Detection and Diagnosis

Men with Low PSA Levels Can Still Have Prostate Cancer



Histological slide showing prostate cancer.

In an NCI study, 15 percent of men with prostate-specific antigen (PSA) scores lower than 4.0 ng/ml—the current threshold score for a "normal" finding—were still found to have prostate cancer.

NCI's 7-year Prostate Cancer Prevention Trial (PCPT) enrolled nearly 19,000 men age 55 and older to study the potential of finasteride for preventing prostate cancer. Half of the men received finasteride—which was ultimately shown in this trial to reduce the prevalence of prostate cancer by 25 percent—and the other half received a placebo. All trial participants underwent annual PSA screenings and digital rectal exams. Men who were found to have a PSA level higher than 4.0 ng/ml or an abnormal digital rectal exam during an annual check-up were recommended for prostate biopsy.

At the end of the trial, all remaining participants were asked to undergo a prostate biopsy. Scientists performed these biopsies to estimate the accuracy of digital rectal exam and PSA testing—separately and together—in detecting whether a man has prostate cancer.

Among the 2,950 men in the placebo group who never had a PSA score above 4.0 ng/ml or an abnormal digital rectal exam, prostate cancer was diagnosed in 449 individuals (15.2 percent). Among the 449 cancers, 67 (14.9 percent) were assigned a Gleason score—a pathologic assessment of prostate cancer cells that is used to predict clinical outcome—of seven or higher, indicating a potentially aggressive form of the disease.

As expected, the lower the PSA value, the fewer the cases of prostate cancer found, and the lower the risk of detecting high-grade disease. However, some cases of prostate cancer (10 percent) were detected in men with the lowest PSA levels—less than 0.6 ng/ml. These results point to the need for better methods to detect prostate cancer and to distinguish slow-growing, clinically unimportant cancers from aggressive forms of the disease that require treatment.

"The challenge now is to develop biomarkers to identify the prostate cancers that need treatment," says Howard L. Parnes, M.D., of NCI's Division of Cancer Prevention (DCP). "The way we think about using the PSA test has changed," he adds. "This study tells us that there is no magic threshold below which a man can be assured of having no risk of

prostate cancer nor above which a biopsy should automatically be performed. A man's decision to have a prostate biopsy requires a thoughtful discussion with his physician, considering not only the PSA level, but also his other risk factors, his overall health status, and how he perceives the risks and benefits of early detection."

Thompson I, Pauler D, Goodman P, Tangen C, Lucia M, Parnes H, Minasian L, Ford L, Lippman S, Crawford E, Crowley J, Coltman, C. Prevalence of prostate cancer among men with a prostate-specific antigen level less than or equal to 4.0 ng/milliliter. *New England Journal of Medicine*, May 27, 2004; 350(22):2239-2246.

Thompson I, Ankerst D, Chi C, Lucia M, Goodman P, Crowley J, Parnes H, Coltman, Jr, C. Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/mL or lower. *Journal of the American Medical Association*, July 6, 2005;294(1):66-70.

National Studies Examine Usefulness of CT Scans for Early Detection of Lung Cancer

In a 1-year pilot program known as the Lung Screening Study (LSS), scientists convincingly demonstrated the feasibility of conducting a randomized, clinical trial comparing the effectiveness of low-dose spiral computed tomography (LDCT) and chest X-ray (CXR) for detecting early lung cancer. This finding laid the groundwork for the landmark National Lung Screening Trial (NLST), an 8-year clinical trial that is now being conducted at 30 sites nationwide. NLST is assessing whether LDCT screening in people at high risk for lung cancer can more effectively reduce mortality from this disease than screening with CXR.

LSS enrolled 3,318 persons between the ages of 55 and 74 years who had a history of heavy cigarette smoking (at least 30 packs per year) and who were either currently smoking or had quit within the previous 10 years. The participants were randomly assigned to screening with one of the two methods. In the initial screening with LDCT, 325 individuals (20.5 percent) had results that suggested the possibility of cancer and the need for medical follow-up. Additional testing confirmed lung cancer in 30 (9.2 percent) of these individuals. In comparison, 152 individuals (9.8 percent) who received CXR as the initial screening had positive findings and, with follow-up, seven (4.6 percent) of them were found to have lung cancer.

LSS findings confirmed that the enrollment of high-risk patients in a lung cancer screening trial could be accomplished quickly enough to allow a clinical study to be completed in a timely fashion. The study also established that high-risk patients were willing to be randomly assigned to receive either type of screening and to undergo appropriate examinations and

follow-up. Finally, the study's findings provided the first set of baseline screening results and detection rates for a clinical trial using LDCT screening. LSS did not evaluate whether these screening techniques reduce cancer mortality—this question will be addressed through NLST.

NLST is a collaborative effort between the NCI and the American College of Radiology Imaging Network (ACRIN). NLST researchers enrolled more than 53,000 smokers and former smokers between the ages 55 and 74, exceeding the original goal of 50,000 participants established when NLST was launched in 2002. Remarkably, NLST recruitment was completed ahead of schedule.

In addition to assessing the effect of these screening approaches on lung cancer mortality, NLST scientists also will evaluate quality-of-life issues, cost effectiveness of screening methods, and the impact of screening with either technique on smoking cessation behaviors. Furthermore, researchers are collecting and storing tissue samples from participants so they can be used in future studies of biomarkers. Final data analysis for NLST is expected by 2009.

Gohagan J, Marcus P, Fagerstrom R, Pinsky P, Kramer B, Prorok P. The Lung Screening Study of the National Cancer Institute. *Chest*, July 1, 2004; 126(1):114-121.

Gohagan J, Marcus P, Fagerstrom R, Pinsky P, Kramer B, Prorock P, Ascher S, Bailey W, Brewer B, Church T, Engelhard D, Ford M, Fouad M, Freedman M, Gelmann E, Gierada D, Hocking W, Inampudi S, Irons B, Johnson C, Jones A, Kucera G, Kvale P, Lappe K, Manor W, Moore A, Nath H, Neff S, Oken M, Plunkett M, Price H, Reding D, Riley T, Schwartz M, Spizarny D, Yoffie R, Zylak C. Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer. *Lung Cancer*, January, 2005; 47(1):9-15.

New Imaging Method May Improve Accuracy of Breast Cancer Biopsies

A new imaging method developed at NCI has the potential to spare many breast cancer patients from axillary lymph node dissection—surgery to remove a large number of lymph nodes from the armpit area closest to the breast tumor—to make it much easier for patients and their doctors to choose the right therapy.

Today, the decision to undergo radiation and/or chemotherapy after surgery is based on the size of the tumor and whether tumor cells have spread from the breast to the axillary lymph nodes. The first lymph node that lymph from the area around a breast tumor drains into is called the "sentinel node," and this lymph node is, therefore, the first place that cancer cells are likely to spread. If cancer cells have not spread to the sentinel node, it is unlikely that they have spread to any other lymph nodes, indicating that axillary dissection is not necessary.

Until now, determining whether the sentinel lymph node contains any cancer cells has been an inexact science, and surgeons have had to biopsy several nodes to determine if they contain cancer cells. The new experimental imaging method is called real time, micromagnetic resonance mammolymphangiography (MRml). It uses a tiny contrast agent that is perfectly sized to be taken up slowly and retained in normal lymph node tissue to help visualize lymph nodes that contain metastatic cancer cells. Cancer cells do not absorb the agent. Therefore, lymph nodes that contain cancer cells do not show up in the image as completely "filled" with the contrast agent, whereas nodes free of cancer cells do.

The researchers hope the new imaging method, which is being evaluated in animal studies, will enable doctors to identify affected lymph nodes with greater clarity, thereby allowing surgeons to perform less invasive procedures.

Unlike current biopsy approaches, MRml is noninvasive and the special contrast agent it employs does not expose patients or doctors to radiation. MRml scans lymph node drainage in real time, enabling doctors to locate the sentinel lymph node and the next affected node(s). That will make it easier for them to decide which nodes, if any, to remove. Researchers from NCI's Molecular Imaging Program have also designed MRml to allow doctors to view the specific locations of lymph nodes in three dimensions, making surgery easier to perform.

A clinical trial of MRml is planned after the completion of safety trials in animals.

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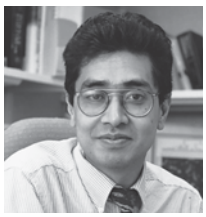
Artificial Intelligence Program Predicts Outcome for Patients with Neuroblastoma

Using gene profiling and artificial neural networks (ANN), NCI scientists—in collaboration with colleagues from Germany and Australia—have developed an innovative approach to successfully predict the clinical outcome of infants and children diagnosed with neuroblastoma, a cancer that usually originates in the tissue of the adrenal gland. This new approach using "artificial intelligence" technology may prove to be a valuable tool that one day can help guide treatment decisions and predict long-term survival prospects for this group of pediatric patients.



Javed Khan

In developing this new approach, Javed Khan, M.D. and his team in NCI's Pediatric Oncology Branch first established global genetic profiles of primary neuroblastoma tumors using samples of tumors from 49 patients with neuroblastoma and a known clinical outcome—either good (event-free survival for more than three years) or poor (death due to disease). Next, the scientists used an adapted ANN algorithm—a specialized pattern-recognition program modeled after the human brain—to identify patterns in gene expression. They found that the ANN could predict the clinical outcome from any gene profile of the 49 patients with an accuracy of about 88 percent.

The first gene profiles consisted of more than 25,000 genes. In an effort to simplify the test and optimize the profiles, the investigators tried to find the minimum number of genes that could serve as a "predictor set" to help predict clinical outcome. Using the neural networks, they identified a set of 19 genes for the predictor set. When looking only at these 19 genes, the ANN accurately predicted a patient's outcome in 95 percent of the tests.

Currently, neuroblastoma patients are divided into high-, intermediate- and low-risk groups based on age, histologic factors, and the copy number of a gene called *MYCN*. Overexpression of this gene alone indicates poor prognosis. This new tool can provide physicians with a way to more accurately distinguish high- and low-risk patients, and to identify high-risk patients who do not have overexpression of the *MYCN* gene. Moreover, because the survival rate for patients in the high-risk group is less than 30 percent—and physicians have no way of knowing which high-risk patients will respond to standard therapy—this new approach can help physicians identify patients who may benefit from new therapeutic approaches.

Khan and colleagues plan to test the ANN strategy on a larger group of tumor samples. They are also trying to determine the functions of the top "predictor" genes, only some of which have been previously associated with neuroblastoma. Several of the genes produce proteins that may circulate in the blood, opening the possibility for a blood test as another means of estimating risks for such patients.

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MRI scans on a lightbox. Credit: G. Tompkinson/ Photo Researchers, Inc.

State-of-the-Art Medical Imaging Technologies are Transforming Cancer Detection and Treatment

The latest advances in medical imaging hold enormous potential for helping physicians detect cancers at earlier and more treatable stages—before metastasis begins—which can dramatically improve the odds of survival.

One such advance is "digital" mammography. Digital mammography takes an electronic image of the breast and stores it directly in a computer. Unlike conventional, film-based mammography, this new technology allows recorded data to be enhanced, magnified, or manipulated so images can be further evaluated by a radiologist and subtle differences in tissues can be noted. Digital images can also be stored and retrieved electronically, making long-distance consultations with other mammography specialists easier. As with conventional images, digital images can be printed on film as well.

The American College of Radiology Imaging Network (ACRIN), supported by NCI, is conducting a clinical trial—the Digital Mammography Imaging Screening Trial (DMIST)—to compare the diagnostic power of digital mammography to conventional, film-based mammography in detecting breast cancer lesions. This large-scale study screened a total of 49,529 asymptomatic women at 35 medical centers in the United States and Canada.

DMIST compared the diagnostic performance of digital versus screen-film mammography for relative sensitivity, specificity, and positive- and negative-predictive values. Researchers examined several factors, including whether digital mammography may be more effective in detecting cancers in women with dense breasts because it has improved contrast resolution. In addition, they used digital mammography machines manufactured by four different companies to broaden the applicability of this study.

Initial findings from the DMIST study were announced in September 2005 and confirmed earlier indications that digital mammography can be more accurate for women with dense breasts. Several other groups of women benefited from undergoing screening with digital mammography instead of film, including women under age 50 and pre- and perimenopausal women. The findings also showed that, for the entire population of women studied, digital and film mammography had very similar screening accuracy.

NCI is also developing new methods to improve the use of imaging technologies in clinical trials for new cancer treatments. The Institute's Cancer Imaging Program has spearheaded a collaboration among clinical investigators, clinical study design experts, and industry representatives to forge a standardized clinical trials design for imaging-guided interventions (IGI) and other therapies using imaging devices.

In another effort, NCI has entered into an agreement with General Electric Medical Systems to develop the radiopharmaceutical imaging agent F-18 fluorodeoxythymidine (FLT) for use in positron emissions tomography (PET) scans. This agreement may serve as a template for developing other radiopharmaceuticals.

NCI has also developed a contract mechanism to support early clinical trials focused on evaluating the safety and preliminary effectiveness of promising imaging probes, ligands, radiopharmaceuticals, and contrast agents. This contract method currently is being used to conduct studies of three imaging agents. Two of the test agents are used in magnetic resonance imaging (MRI)—one to image brain tumors and a second to assess lymph node involvement in metastatic disease. A third test agent is being evaluated in PET scanning to assess cancer cell proliferation.

Perhaps the most cutting-edge research is taking place with the use of microscopic devices that employ nanotechnology in combination with imaging methods to observe the earliest stages of the cancer process and tumor biology. Scientists are now able to monitor processes at the molecular level, such as the erosion of telomeres—specialized DNA and protein complexes at the end of chromosomes that are linked to the initiation of some tumors. The increasing capacity to apply molecular imaging techniques to track cellular processes will dramatically expand the repertoire of potential biomarkers for cancer prevention, detection, prediction, and treatment.

Ultrasound transducer. Credit: David Gifford/ Photo Researchers, Inc.

Ultrasound May Improve Screening for Breast Cancer in High-Risk Women

A unique partnership involving the NCI, the American College of Radiology Imaging Network (ACRIN), and the Avon Foundation is evaluating the role of ultrasound as a supplement to mammography in screening women with dense breast tissue who are at high risk for breast cancer.

The main objective of this multi-center clinical trial, which will enroll 2,800 women, is to provide guidance to patients and practitioners about the role of breast ultrasound screening and the associated risk of an unnecessary biopsy.

"Why isn't ultrasound routinely performed to supplement mammography in women with dense breasts?" asks ACRIN's Wendie Berg, M.D., Ph.D., principal investigator for the study. "The short answer is that, in some centers, it already is. The data are compelling, indicating that breast cancer detection will be improved and that the cancers found are usually those with good prognoses."

Data are being collected at 22 institutions across the United States. Study participants will receive annual mammography and radiologist-performed ultrasound screening, with both tests performed and interpreted independently, when they enter the trial and again at 12- and 24-month time points.

In addition to the primary goal of evaluating the contribution of supplemental ultrasound, the study will also look at the time and resources required to perform ultrasound screening, including the induced costs of biopsy and short-interval follow-up. Training modules developed for the study will help ensure consistency among the ultrasound readers across the United States. If readers can identify subtle lesions and recognize the vast majority of cancers in the training materials, they should be able to use these techniques with their patients. These training materials will also be widely available to practicing radiologists.

The Avon Foundation also supported the training of an ACRIN-Avon Fellow in clinical trials of breast imaging. This two-year fellowship provides training in the development, implementation, and analysis of clinical imaging research.

The development of more efficient and effective cancer treatments that target cancer cells while leaving surrounding healthy tissue unharmed is at the heart of NCI's research agenda. NCI supports a broad portfolio of treatment studies. We strive to develop well-tolerated, individualized therapies that are tailored to specific features of a patient's cancer. We seek to understand the molecular mechanisms that lead to resistance to treatment drugs and to develop strategies to combat that resistance. Researchers apply biomedical technologies such as genomics, proteomics, nanotechnology, vaccine technologies, and molecular imaging to accelerate the development and increase the scope of targeted treatment approaches. The following examples spotlight the progress NCI made in 2004 in cancer treatment research.

4

Developing Effective and Efficient Treatments

Novel Drug Therapy Shows Promise Against Metastatic Colon and Kidney Cancers

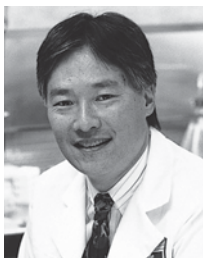
The antiangiogenesis drug bevacizumab (Avastin®), which was approved for the treatment of metastatic colon cancer in 2004, is also showing early promise against advanced kidney and other difficult-to-treat cancers.

Bevacizumab was the first drug to be approved in the United States that works by blocking the formation of new blood vessels in tumors—a process known as tumor angiogenesis. Tumor angiogenesis is needed for tumors to get the oxygen and nutrients necessary for continued growth and survival.

Bevacizumab was proven safe and effective in a large, randomized, controlled clinical trial, significantly extending the survival of patients with metastatic colon cancer. In the trial, 813 patients were randomly assigned to treatment with bevacizumab (402 patients) or a placebo (411 patients). All patients were treated additionally with the drugs irinotecan, 5-fluorouracil, and leucovorin (IFL). The median survival of the patients in the bevacizumab plus IFL group was 20.3 months, compared with a median survival of 15.6 months for patients in the placebo plus IFL group. This difference translates into a 34 percent reduction in the risk of death for patients treated with bevacizumab compared to patients treated with placebo.

"This result was an important milestone in cancer management," says Fairooz Kabbinavar, M.D., a researcher at UCLA's Jonsson Comprehensive Cancer Center and senior author of the trial report. He noted that, in just four years, survival for patients with advanced colorectal cancer nearly doubled from 1 year to 2 years. "And Avastin® has manageable toxicity," he notes. "So patients not only live longer, but their quality of life is also maintained."

Bevacizumab is now being tested in more than 20 clinical trials for the treatment of breast, prostate, cervical, ovarian, pancreatic, and lung cancers, as well as mesothelioma and several types of leukemia. In one study completed by scientists in NCI's Center for Cancer Research, 116 patients with metastatic clear-cell carcinoma of the kidney were randomly assigned to receive either high-dose (10 mg per kilogram body weight) or low-dose (3 mg per kg body weight) bevacizumab or a placebo. The median time to disease progression for both groups of bevacizumab-treated patients was significantly longer than that observed for the patients treated with placebo. For patients treated with high-dose bevacizumab, the median time to disease progression was almost double that of the placebo-treated patients (4.8 months versus 2.5 months).



James C. Yang

"Bevacizumab seems to have only modest benefits in some of these early studies, but this field is in its infancy, and identifying which angiogenesis inhibitors are producing the expected effects in patients is very important," says NCI's James C. Yang, M.D., lead author of the kidney cancer trial report. "Use of a single drug may have limited impact, but everyone in this field expects that combining several with proven activity will be much more effective."

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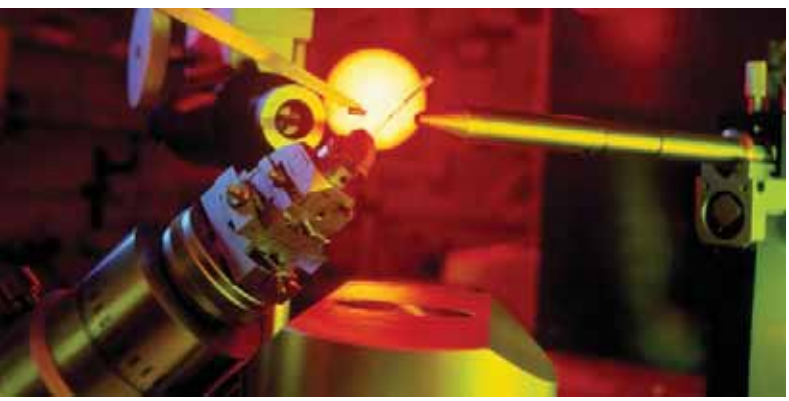
New Drug Designed to Overcome Resistance to Gleevec®

Researchers have designed a new drug that may prove effective in treating most patients with chronic myeloid leukemia (CML) whose cancers have become resistant to the drug imatinib (Gleevec®).

When it was first approved by the Food and Drug Administration for the treatment of CML in 2002, imatinib was heralded as a major breakthrough in the search for treatments that target the specific molecular changes in cells that cause them to become cancerous. Imatinib blocks the activity of an abnormal protein called Bcr-Abl that causes almost all cases of CML. Unfortunately, the cancer cells in some patients treated with imatinib become resistant to the drug. This resistance is caused by mutations in Bcr-Abl that prevent imatinib from binding to the protein.

According to Robert Mufson, Ph.D., chief of NCI's Cancer Immunology and Hematology Branch in the Division of Cancer Biology, "The majority of patients who initially respond well to imatinib therapy are at risk of developing resistance to the drug and suffering relapse—even those whose disease may appear to be in complete remission."



X-ray diffraction crystallography. Credit: James King-Holmes/ OCMS/Photo Researchers, Inc.

Once resistance to imatinib became recognized as a problem, scientists at Bristol-Myers Squibb made several different versions of another drug known to inhibit Bcr-Abl and chose one—BMS-354825—for further study. In collaboration with researchers at the David Geffen School of Medicine and Jonsson Comprehensive Cancer Center at the University of California at Los Angeles, they discovered that BMS-354825 was effective against 14 of 15 imatinib-resistant variants of Bcr-Abl. When tested in mice, the new drug increased the survival times of those that had leukemias caused by Bcr-Abl. BMS-354825 also inhibited the proliferation of CML cells obtained from patients with imatinib-resistant disease but did not inhibit the proliferation of healthy bone marrow cells.

Several early-phase clinical trials sponsored by NCI and Bristol-Myers Squibb are underway to test the safety and the effectiveness of BMS-354825 in patients with CML that is resistant to imatinib. This new drug could potentially benefit up to 80 to 85 percent of CML patients with imatinib-resistant disease, according to researchers, and it might be used in combination with imatinib or other Bcr-Abl inhibitors to treat CML and prevent the emergence of drug resistance.

A key technology used in designing and understanding the mechanism of action of targeted therapies such as imatinib and BMS-354825 is X-ray crystallography. This technique allows scientists to create three-dimensional images of the structure of proteins and other biological molecules. They can use these images to determine how new drugs might interact with the molecules at the atomic level.

The promise of X-ray crystallography has led NCI to collaborate with the National Institute of General Medical Sciences to construct and operate a state-of-the-art X-ray crystallography experimental facility at the Argonne National Laboratory in Chicago. Scientists will use this facility to study specific interactions between molecules to identify potential drug targets and candidate drugs and to fine tune these agents to improve their clinical performance.

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Chemotherapy After Surgery Improves the Outlook for Early Stage Lung Cancer

The outlook for patients with early stage lung cancer has been substantially improved thanks to two clinical trials that showed chemotherapy after surgery can significantly increase the long-term survival of individuals diagnosed with this disease.

One trial was led by the Cancer and Leukemia Group B (CALGB), an NCI-supported clinical trials cooperative group. Two other NCI-supported cooperative groups—the North Central Cancer Treatment Group (NCCTG) and the Radiation Therapy Oncology Group (RTOG)—also participated. In the trial, 344 patients diagnosed with stage IB non-small cell lung cancer (NSCLC) had surgery to remove their tumors and were then randomly assigned to receive either no additional treatment or to receive chemotherapy with the drugs paclitaxel and carboplatin. Stage IB NSCLC is defined as a tumor size of more than three centimeters in diameter or a tumor that has invaded the lung's surface lining but has not invaded any nearby lymph nodes.

Among the patients treated with chemotherapy, 71 percent survived at least four years, compared with 59 percent survival among the patients not treated with chemotherapy. At the time the trial results were announced at the 2004 annual meeting of the American Society of Clinical Oncology (ASCO), 19 patients in the chemotherapy group had died of lung cancer compared with 34 patients in the group not treated with chemotherapy. These results were statistically significant.

The second trial was led by the National Cancer Institute of Canada, with the participation of three NCI-supported clinical trial cooperative groups—CALGB, the Southwest Oncology Group (SWOG), and the Eastern Cooperative Oncology Group (ECOG). In the trial, 482 patients diagnosed with stage IB or stage II NSCLC were randomly assigned after surgery to either no additional treatment or chemotherapy with the drugs vinorelbine and cisplatin.

After five years, 69 percent of the chemotherapy treated patients had survived, compared with 54 percent survival among the patients not treated with anticancer drugs. The median survival time for patients in the chemotherapy group was 94 months, compared with a median survival of 73 months for patients in the group that was not treated with chemotherapy. These results were statistically significant and were also announced at the 2004 ASCO annual meeting.

"The convincing findings from these two studies have already changed the way lung cancer is treated," says Gary Strauss, M.D., M.P.H., of Rhode Island Hospital and Brown Medical School and leader of the CALGB trial of paclitaxel and carboplatin. "We have needed something to work for lung cancer," he adds, "which, unlike breast cancer, has been associated with such a high death rate even when caught at an early stage."

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Cell culture used for the production of monoclonal antibodies. Credit: James Holmes/ CELLTECH LTD/Photo Researchers, Inc.

Monoclonal Antibody Triggers Cancer Cell Death

Scientists at the University of Alabama at Birmingham (UAB) have developed a mouse monoclonal antibody called TRA-8 that attaches to "death receptors" on the surface of cancer cells and triggers a process of apoptosis, or cell suicide.

Although normal cells also have death receptors on their surface, they are largely resistant to the death-inducing effects of TRA-8. Specifically, TRA-8 binds to a protein called death receptor 5 (DR5). DR5 is a member of a family of cell surface receptors called the "tumor necrosis factor superfamily of death receptors." These proteins play an important role in normal embryonic development and the immune system. When activated, the receptors trigger apoptosis.

In a series of investigations reported in 2003, 2004, and early 2005, the scientists—led by Donald J. Buchsbaum, Ph.D., director of UAB's Division of Radiation Biology—found that TRA-8 could induce apoptosis in cancer cells of the breast, brain, colon, prostate, ovary, pancreas, and cervix.

"The antibody has also shown impressive efficacy against a variety of human tumors grown in animal models," says Buchsbaum. "That has been enhanced substantially by combining it with chemotherapy or radiation therapy. Chemotherapy and radiation therapy alter proteins that work to inhibit cell suicide, enabling TRA-8 to trigger cell death more effectively," Buchsbaum explains.

This research has been supported by UAB's participation in NCI's Specialized Programs of Research Excellence (SPORE) in Breast, Ovarian, and Pancreatic Cancer.

Sankyo Co., Ltd., based in Tokyo, has licensed TRA-8 and developed a "humanized" version of it. The company has begun testing its new version in animal models to gauge its safety. If the early tests are successful, clinical trials of humanized TRA-8 could begin in the near future.

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First Evidence Found That Chemotherapy Extends Life in Advanced Prostate Cancer

Results from two large clinical trials have shown that chemotherapy with the drug docetaxel (Taxotere®) can help extend the lives of men with metastatic prostate cancer that is no longer responding to hormonal therapy.

Initially, prostate cancer requires male hormones (androgens) to grow, and it is often treated by methods aimed at lowering androgen levels in the body. Treatments that alter hormone levels or activity are referred to as "hormonal therapies." Eventually, however, prostate cancer becomes "refractory," or resistant, to hormonal therapy. Before these trials, men with hormone-refractory, metastatic prostate cancer were considered to have "end-stage" disease and received only palliative care to relieve pain and other symptoms of the disease.

One of the new trials was led by the Southwest Oncology Group (SWOG), which is an NCI-supported clinical trials cooperative group. In the trial, 770 men were randomly assigned to treatment with the drugs docetaxel and estramustine or to palliative care with the drugs mitoxantrone and prednisone. The treatments were repeated at 3-week intervals. The researchers found that treatment with docetaxel and estramustine lengthened the median survival time of patients by two months (17.5 months versus 15.6 months) and the median time to disease progression by three months (6.3 months versus 3.2 months). These results were statistically significant.

"Docetaxel is definitely a new standard of care," says Daniel Petrylak, M.D., associate professor of medicine at Columbia University's College of Physicians and Surgeons and one of the trial's lead investigators. "Future studies will show if docetaxel can be combined with different agents to further improve survival and if docetaxel is effective in treating earlier stage prostate cancers."

The second trial was sponsored by Aventis Pharmaceuticals, Inc., the maker of docetaxel. A lead investigator for this trial was Mario Eisenberger, M.D., of the Sydney Kimmel Comprehensive Cancer Center at Johns Hopkins University. In the trial, 1,006 patients were randomly assigned to treatment with one of two regimens of docetaxel—once a week or once every three weeks—or to palliative care with mitoxantrone given once every three weeks. The patients in all three groups were treated with prednisone twice daily.

The Aventis study demonstrated a statistically significant improvement in median survival when docetaxel was administered every three weeks compared to palliative treatment with mitoxantrone (18.9 months versus 16.5 months), which reflects a decreased risk of death of 24 percent. The side effects of treatment were mostly moderate and reversible, and the study also showed that approximately half of the patients treated with docetaxel—both on the every three weeks schedule and the weekly schedule—had a greater than 50 percent decline in their prostate-specific antigen (PSA) values, improved pain control, and an improved quality of life compared to patients assigned to receive mitoxantrone and prednisone.

"These results are a reason for celebration as well as for optimism for the future," says Eisenberger. "It is unlikely that estramustine as used in combination with docetaxel in the SWOG study has any significant role, especially in view of increased side effects."

Based on the results of the Aventis trial, the Food and Drug Administration approved docetaxel with prednisone given at three-week intervals as the new standard treatment for men with hormone-refractory, metastatic prostate cancer.

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New Vaccines Activate Immune Responses Against Cancer Cells

A new approach to making cancer vaccines shows promise in stimulating the immune system to attack and destroy cancer cells, leading to disease stabilization—at least temporarily—in some patients with advanced cancers.

Many of the cancer vaccines being tested use viruses to infect patients. These viruses are often modified to carry DNA that contains the genetic code for a protein that is made in abnormally high amounts by cancer cells. When the modified viruses are injected into patients, they infect the patients' cells, and the infected cells start making large amounts of the cancer-associated protein. The infected cells then display all or part of the cancer-associated protein on their surface, where, hopefully, cells of the immune system will see it,

recognize it as "foreign," and mount an immune response against it. If a strong enough immune response is generated, cells of the immune system may then be able seek out and destroy other cells that display the protein—that is, cancer cells anywhere in the body.

One protein that is made in abnormally high amounts by many cancers is called carcinoembryonic antigen (CEA). This protein is also made by some embryonic cells. In adults, the production of CEA is largely turned off, but it is turned back on in cancer cells. Cancers that overproduce CEA include cancers of the gastrointestinal tract—for example, colon and rectal cancers—and cancers of the breast, lung, head and neck, and cervix. In addition, CEA has been linked to cancer spread, or metastasis.

Researchers have been exploring the use of CEA in cancer vaccines for more than a decade. Some of the results demonstrated that the effectiveness of CEA-based vaccines could be enhanced by including the genes for three proteins (B7-1, ICAM-1, and LFA-3), known collectively as TRICOM, into the virus used to make the vaccines. The TRICOM proteins help strengthen immune responses involving white blood cells called cytotoxic T lymphocytes.

On the basis of this information, scientists from Georgetown University Medical Center, Therion Biologics Corporation, and NCI's Laboratory of Tumor Immunology and Biology conducted the first ever clinical trial of vaccines that combine CEA with TRICOM. Two different vaccines were used in this early phase trial—one that used vaccinia virus as the carrier, or "vector"—and one that used fowlpox virus as the vector. Neither virus causes disease in humans.

The scientists enrolled 58 patients with advanced cancers that expressed CEA and injected small groups of them with one or both of the viruses at different concentrations. After 4 months, 23 patients (40 percent) had stable disease and 14 of the 23 patients had stable disease that lasted more than six months. The cancer in one patient was completely undetectable after vaccination.

Jeffrey Schlom

"Patients who received both vaccines in combination in these preliminary studies showed a better response than those who received just one vaccine," notes senior investigator Jeffrey Schlom, Ph.D., of NCI's Laboratory of Tumor Immunology and Biology. "Also, increased survival in this trial was related to an increased immune response to the vaccine. Larger, randomized studies, however, must be conducted to further validate these findings."

NCI researchers are currently conducting additional clinical trials of CEA-TRICOM vaccines and vaccines that contain the gene for a second tumor antigen (MUC-1), in addition to CEA and the TRICOM genes.

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Preclinical Testing Program Created to Identify New Treatments for Childhood Cancers

In 2004, NCI announced a first-of-its-kind laboratory and animal testing program that will evaluate 10 to 15 new agents or combinations of agents each year to identify new treatments for common childhood cancers. The Pediatric Preclinical Testing Program (PPTP) will begin testing its first set of agents in 2005.

The goal of the PPTP is to generate the kind of information that will allow pediatric oncology researchers to make educated, reliable decisions about which new agents should be tested in children with specific cancers. This is critically important because only a limited number of clinical trials can be conducted for any given type of childhood cancer due to the rarity of these cancers. If more effective treatments are to be provided for pediatric cancer patients in the shortest period of time, only agents with the best chance of success should be advanced to clinical trials.

The PPTP is supported by an NCI research contract with St. Jude Children's Research Hospital in Memphis, Tennessee. Peter Houghton, Ph.D., of St. Jude is the principal investigator. Testing will occur at St. Jude and five other sites that have expertise in specific childhood cancers. The other sites include Children's Hospital of Philadelphia, Albert Einstein College of Medicine, Duke University Medical Center, Children's Hospital of Los Angeles, and Children's Cancer Institute Australia. Malcolm Smith, M.D., of NCI's Cancer Therapy Evaluation Program, is the NCI project officer for PPTP.

The predictive capabilities of the PPTP's preclinical tests will be evaluated by comparing the results of PPTP studies with the clinical activity of the tested agents in children, taking into account any differences in the way the agents are absorbed, distributed, metabolized, and eventually excreted by test animals in comparison with children.

NCI also sponsored a workshop in May 2005 to discuss opportunities for public-private partnerships to identify molecular targets specific to childhood cancers and to build on the advances already made in developing targeted therapies for adults.

Mutations in Epidermal Growth Factor Receptor Key to Lung Cancer's Response to Gefitinib

Researchers from Harvard University, Nagoya City University Medical School in Japan, and NCI have discovered mutations in a specific region of the epidermal growth factor receptor (EGFR) gene that appear to explain why some patients with non-small cell lung cancer (NSCLC) respond to targeted therapy with the drug gefitinib (Iressa®).

The protein product of the EGFR gene is overexpressed in 40 to 80 percent of NSCLC tumors—and in other types of cancer—and has, therefore, been considered an attractive candidate for the development of targeted therapies. Gefitinib blocks the EGFR protein's tyrosine kinase enzyme activity, which can initiate both proliferation and survival signals in tumor cells, by binding to a specific site in the protein's tyrosine kinase "domain." Until the discovery of the EGFR gene mutations—which alter the genetic code for the tyrosine kinase domain—researchers were at a loss to explain why some patients with NSCLC are able to respond to gefitinib treatment whereas most patients are not.

In one study reported in 2004, researchers identified mutations in the tyrosine kinase domain coding region of the EGFR gene in tumor samples from eight of nine patients with NSCLC who responded to gefitinib. In contrast, no mutations were identified in tumor samples from seven patients with NSCLC who did not respond to the drug. Similar mutations were found in the tumors of two (8.0 percent) of 25 NSCLC patients who had not been treated with gefitinib. Additional research demonstrated that mutant EGFR proteins had more tyrosine kinase activity than the normal protein and were markedly more sensitive to the inhibitory effects of gefitinib. A second study conducted by the some of the same researchers further showed that the mutant EGFR proteins selectively activated cell survival

signals. The scientists speculated that mutant NSCLC tumor cells may become overly dependent on these survival signals and are, therefore, more prone to dying when these signals are blocked by gefitinib.

A third study reported in 2004 was conducted by an independent group of investigators. These researchers found similar EGFR tyrosine kinase domain mutations in the tumors of five of five patients with NSCLC who had responded to gefitinib and in none of the tumors of four patients with NSCLC who did not respond to the drug. In addition, the researchers found tyrosine kinase domain mutations in tumor samples from 15 (25.9 percent) of 58 Japanese NSCLC patients and one (1.6 percent) of 61 U.S. NSCLC patients who had not been treated with gefitinib. This striking difference in the frequency of EGFR gene mutations in the tumors of Japanese patients compared with U.S. patients is consistent with earlier observations of higher response rates to gefitinib among Japanese NSCLC patients than among NSCLC patients with a predominately European background.

"These studies demonstrate the importance of understanding the molecular mechanisms that underlie sensitivity to a selective inhibitor such as gefitinib," says Judith Mietz, Ph.D., chief of the DNA and Chromosome Aberrations Branch in NCI's Division of Cancer Biology. For clinical trials of targeted therapies, it is not always enough to identify a target and construct a therapeutic molecule; often, the specific mechanism of action must be understood, and patients must be screened to identify the subgroup that will respond. Furthermore, these findings support the idea that there may be ethnic, cultural, and geographic differences in the molecular pathogenesis of NSCLC and other cancers and point to the importance of population diversity in cancer clinical trials.

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NCI seeks to increase 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. Outcomes research looks at the impact of various influences that matter to decision makers, including patients, providers, private payers, government agencies, accrediting organizations, and society at large. These influences affect the extent to which public health programs and health care providers adopt recommended interventions, how successful the interventions are in addressing public health concerns, and how well patients adhere to provider recommendations. Outcomes may be measured in terms of survival, health-related quality of life, satisfaction with care, the performance of the health care system, and the economic burden on individuals or society. The following examples highlight our progress in this area for 2004.

5

Understanding the Factors that Influence Cancer Outcomes

Cancer Outcomes Research Looks at "Real World" Practice Settings

NCI's Cancer Outcomes Research and Surveillance (CanCORS) Consortium project is evaluating the quality of cancer care in this country so that cancer care delivery may be optimized in all practice settings. The goal of this project is to identify the key characteristics of patients, physicians, and clinical practice settings throughout the United States that are associated with the dissemination and implementation of high-quality care necessary to reduce cancer suffering and mortality.

The 5-year CanCORS study—a cooperative effort involving the NCI, the U.S. Department of Veterans Affairs, and the Centers for Disease Control and Prevention—is funding eight teams of investigators from around the United States. The project has recruited about 10,000 patients from diverse geographic and demographic populations, all of whom have been newly diagnosed with lung or colorectal cancer, the two leading causes of cancer death in the United States. CanCORS is an unprecedented effort to gather inclusive data across the spectrum of care from the time of diagnosis through the end of life. To accomplish that goal, the project is using multiple information sources, including claims data; surveys of patients, physicians; and informal caregivers; and detailed reviews of patient medical records.

"Over 20 years of studies show that too many people with cancer in this country don't receive the best possible care for their disease," says Arnold Potosky, Ph.D., director of CanCORS. "If we can collect the necessary evidence regarding why patients do not receive optimal care, then we can apply that information to enhance the dissemination and application of new treatment advances and, ultimately, to improve patients' treatment experiences and reduce cancer deaths."

CanCORS researchers are looking at how characteristics of patients, providers, and health care delivery systems affect the care cancer patients receive to treat and manage their disease. They also are assessing the relationships between cancer-related clinical practices and outcomes such as patients' quality of life and satisfaction with care. Finally, investigators are examining possible reasons for disparities in delivery of cancer care, including biological factors, access issues, financial resources, physicians' practice styles, and patients' individual characteristics, such as age, income, race, and ethnicity.

CanCORS will focus on identifying clinically important differences in cancer treatment and outcomes and on evaluating the reasons for these differences across a broad range of health care providers and organizations. Most quality-of-cancer care studies are unable to fully address the underlying reasons for variations in care delivery and outcomes because they are usually conducted in selected or small populations of patients, use cross-sectional or retrospective designs, or rely on data sources with limited clinical details.

This unique quality-of-cancer care project serves as a valuable complement to ongoing clinical trials that are used to evaluate new cancer therapies, says NCI's Potosky. Those controlled, scientific studies "often do not reflect the real-world attributes of patients and delivery settings," he explains. "One of the key goals of CanCORS' population-based analysis is to determine whether all cancer patients in our complex health care delivery system experience the same care and outcomes as patients who are treated in major referral centers—and most importantly—if not, why not?"

http://healthservices.cancer.gov/cancors

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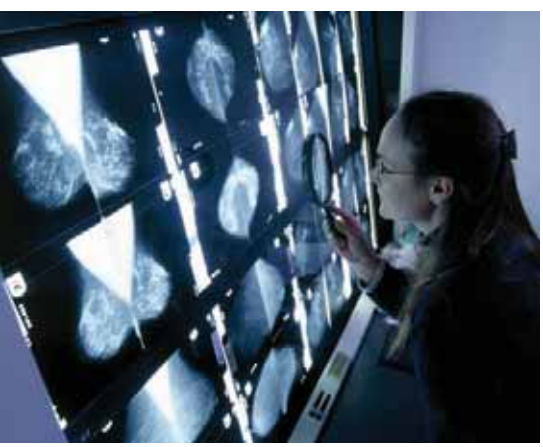

Radiologist studying mammograms on a lightbox. Credit: James King-Holmes/Photo Researchers, Inc.

Lack of Screening Blamed for Late-Stage Diagnoses of Breast Cancer

Women newly diagnosed with breast cancer are much more likely to have late-stage disease if they have not had a screening mammogram previously, according to a study by the NCI and its Cancer Research Network, a consortium of integrated health plans.

Researchers found that 52.1 percent of women diagnosed with late-stage breast cancer had not undergone screening mammography in the 1- to 3-year period before diagnosis compared with 34.4 percent of women who were diagnosed with early-stage disease. Among the women diagnosed with late-stage breast cancer, those who were 75 years of age or older and who were unmarried were less likely to have had a screening mammogram in that time period. Women with less education or from neighborhoods with lower annual incomes were also less likely to have been screened in the 1- to 3-year period before diagnosis.

In this study, the researchers sought to identify where the breast cancer screening process breaks down—screening use, screening detection (the failure of previous mammography to detect cancer), or follow-up (a delayed diagnosis of cancer after an other than "normal/negative" finding on previous mammography)—and to determine where changes in care might have the greatest effect on reducing diagnoses of late-stage breast cancer.

The investigators conducted a retrospective review of three years' worth of medical data for 2,700 women. These 2,700 women came from a population of 1.5 million women who were medically insured through seven different health plans. The researchers identified 1,347 women, age 50 years and older, who had been diagnosed with late-stage breast cancer (case subjects) and an equal number of women who had been diagnosed with early-stage breast cancer (control subjects) between 1995 and 1999. Late-stage breast cancer was defined as metastatic cancer or a primary tumor size of at least three centimeters.

"It was surprising to see the high proportion of women with late-stage cancer—about half—who had not been screened even though they had access to care," said Stephen H. Taplin, M.D., the study's lead author and a senior scientist with NCI's Division of Cancer Control and Population Sciences.

To improve breast cancer outcomes, the investigators state that top priority should be placed on using proven promotion strategies, such as mail and telephone reminders, to reach women age 50 years or older who have not had a mammogram within the last two years. "Health plans can design approaches to communicate with those at highest risk for poor outcomes, such as mailing invitations to women to ensure that the screening option has been presented," Taplin suggests.

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As interventions and technologies become more sophisticated, the cancer community must build upon research evidence to continually enhance the quality, safety, and appropriateness of care. NCI pursues this vision by supporting the efforts of public health programs, primary care practitioners, oncologists, and those who care for the needs of cancer patients, survivors, and their families. We are working for the consistent and equitable delivery of the full range of evidence-based interventions that are safe, patient centered, effective, timely, and efficient. The following advances spotlight quality of care research to reduce treatment side effects and to improve palliative care.

6

Improving the Quality of Cancer Care

Drug Protects Against Heart Damage Caused by Treatment for Childhood Leukemia

The drug dexrazoxane (Zinecard®) can prevent or reduce heart damage in children with acute lymphoblastic leukemia (ALL) who are being treated with the chemotherapy drug doxorubicin, according to a report published by the Dana-Farber Cancer Institute ALL Consortium.

ALL is the most common type of cancer diagnosed in children. Combination chemotherapy with doxorubicin and other anticancer drugs is a highly effective treatment for this disease. Although doxorubicin successfully kills cancer cells, it can unfortunately also damage the heart—most likely by causing the formation of toxic chemicals called free radicals in heart tissue. Many children treated with doxorubicin have long-term heart problems and a significantly increased risk of death from heart-related causes.

The researchers conducted a clinical trial in which newly diagnosed, untreated patients with childhood ALL were randomly assigned to one of two treatment groups. One group, which contained 101 patients, was treated with doxorubicin alone—the standard treatment for ALL. The other group, containing 105 patients, was treated with the drug dexrazoxane followed immediately by treatment with doxorubicin. In earlier studies, dexrazoxane had been shown to protect the hearts of adults treated with doxorubicin.

The researchers analyzed blood samples collected from both groups of patients before, during, and after treatment with doxorubicin. They measured blood levels of a protein called troponin T, which is released by the heart when it is damaged. The blood tests revealed that 50 percent of the children treated with doxorubicin alone had elevated levels of troponin T in their blood, compared with 21 percent of the children who were treated with dexrazoxane followed by doxorubicin.

Importantly, the researchers also noted that, after a median follow-up of more than two and a half years, there was no indication that dexrazoxane treatment reduced the effectiveness of doxorubicin therapy.

"That dexrazoxane can actually protect against cardiac toxicity in children with cancer is an important finding toward better treatment of these children to promote survival and long-term quality of life," says Malcolm A. Smith, M.D., associate branch chief for pediatrics

in NCI's Cancer Therapy Evaluation Program. "However, we still need to be more certain that, while dexrazoxane is protecting the heart cells, it's not protecting the cancer cells, as well." Data from other studies addressing this issue are expected to be available within two years.

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New Drug Relieves Painful Side Effects of Cancer Treatments

In December 2004, the FDA approved palifermin (Kepivance®)—a new drug for treating the sometimes excruciatingly painful mouth sores and ulcers associated with oral mucositis, a common side effect of high-dose chemotherapy and radiation.

Palifermin was approved for the treatment of oral mucositis in people with blood-system cancers (leukemia, lymphoma, or multiple myeloma) who are being treated with intensive chemotherapy and radiotherapy followed by stem cell transplantation. Palifermin is a recombinant version of keratinocyte growth factor (KGF), a naturally occurring human protein that was first purified and studied by NCI scientists. The same NCI scientists were the first to produce biologically active recombinant KGF. The FDA's approval was based on the results of a randomized clinical trial that was conducted at several NCI-designated Cancer Centers and other institutions and was sponsored by the biotechnology company Amgen.

The trial involved 212 patients who were randomly assigned to receive either palifermin or a placebo intravenously during the course of their cancer treatment. Those who received palifermin had fewer mouth sores than those in the placebo group; reported fewer complications such as difficulty eating, drinking, talking, or sleeping; needed fewer painkilling drugs for mouth sores; and did not develop as many serious infections.

"The drug likely acts on at least two levels," says Jeffrey Rubin, M.D., Ph.D., of NCI's Center for Cancer Research. "It stimulates the proliferation of normal tissue, which thickens the mucosal barrier to ward off the toxic effects of cancer treatment, while also reducing the rate of normal cell death by means that include activating antioxidant enzymes."

Despite a theoretical risk that palifermin could protect malignant cells in some cancers—in the same way it protects normal tissue—there is no clinical evidence of this kind of tumor-protective effect. Palifermin is now being tested for its potential to bring relief from the side effects of combination chemotherapy and radiation therapy in patients with non-small cell lung cancer and head and neck cancers.

Meanwhile, participants in the original trial that was used as the basis for the FDA's approval are being followed long-term to assess the potential risk that palifermin could promote the formation of secondary cancers, as well as to collect additional safety data.

Ultimately, Rubin notes, the hope is that by tackling the onerous side effects of existing cancer treatments, drugs like palifermin can enhance the primary treatments' effectiveness by allowing use of higher doses without serious toxic reactions.

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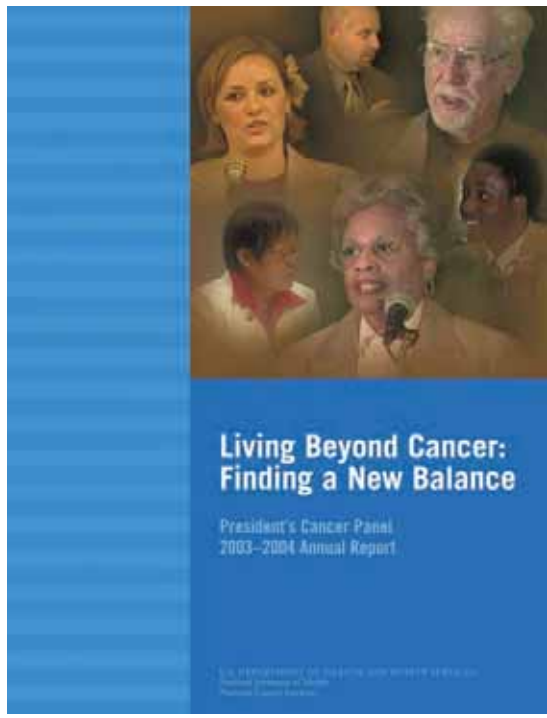
Advances in our ability to detect, treat, and support cancer patients have turned this disease into one that is chronic, or readily managed, for many and curable for increasing numbers. While the ultimate goal of eliminating cancer altogether continues to be our long-term commitment, the capacity to dramatically reduce the suffering caused by cancer is within our immediate grasp. The following 2004 scientific and program advances highlight our progress in predicting who is at risk for adverse health outcomes, developing interventions for treatment effects, and exploring the impact of cancer on family members of patients and survivors.

7

Improving the Quality of Life of Cancer Survivors

Living Beyond Cancer: Finding a New Balance

With their treatment behind them and their bodies cancer-free, the nearly 10 million survivors of cancer in America today still face many physical, psychological, and social challenges. The President's Cancer Panel spells out recommended action steps to address the challenges of cancer survivorship in its report on *Living Beyond Cancer: Finding a New Balance*. The report was presented on June 2, 2004 to the National Cancer Advisory Board, which advises and makes recommendations to the U.S. Secretary of Health and Human Services and the NCI Director on activities carried out by NCI.



"For so long, we thought if there was no longer any evidence of cancer, then everything was all right," says LaSalle D. Leffall, Jr., M.D., chair of the panel that issued the report and professor of surgery at the Howard University College of Medicine. "The truth is that the end of treatment does not represent the end of the problems that people face."

The President's panel held five hearings between May 2003 and January 2004, during which survivors, caregivers, community advocates, health professionals, researchers, and others shared compelling stories about post-cancer physical problems such as infertility and second cancers. They also testified about the psychological and social problems they face, including depression, fear of relapse, and difficulties qualifying for life insurance and other types of financial protection.

In response, the President's Cancer Panel issued several key recommendations:

- Upon discharge from cancer treatment, every patient should be given a record of care already received and important disease characteristics, along with a follow-up care plan.
- Procedures should be established to inform patients and caregivers of their rights to legal and regulatory protections.
- Efforts should be enhanced to educate patients, survivors, families, and health care providers about cancer treatment and survivorship issues.
- Survivors and caregivers should be counseled about common cancer-related psychosocial effects and available support services.
- Attention should be paid to correcting inadequacies in insurance coverage for people with a cancer history.

The President's panel also recommended specific proposals focused on survivors who are diagnosed at various stages of life. For former childhood cancer patients, the panel report addressed issues such as school re-entry and the transition to adult medical care status.

"When cancer organizations, policy makers, and others look at this report to the President, we hope they will say to themselves, 'We must be there to support cancer survivors for the rest of their lives—not just until their body is free of the disease,'" Leffall notes.

NCI's Office of Cancer Survivorship (OCS) cooperated with the President's Cancer Panel to release *Living Beyond Cancer: Finding a New Balance* and has led the Institute's efforts in addressing the report's recommendations. OCS supports and promotes research that addresses the long- and short-term effects of cancer and its treatment. Survivorship research focuses on the physical, emotional, social, and financial outcomes that occur after cancer survivors have completed their treatment. OCS's goal is to optimize the health and well-being of all persons living with a history of cancer.

"Having survivorship acknowledged as an important issue within the nation's premiere cancer research institute has created a place for larger discussion of and scientific attention to the potential human costs of cure," says Julia H. Rowland, Ph.D., director of OCS.

Findings from one OCS-funded project showed that a small group of women diagnosed with breast cancer who were given a behavioral-stress management intervention were more likely than women not given the intervention to see some positive aspects to being diagnosed with breast cancer (such as closer relationships with family members) and experienced a slight increase in immune function, leading to a lower risk of infection. Another study found that survivors of head and neck cancers are likely to have life-long difficulty communicating because treatments have compromised their speech, which causes a significant loss of quality of life because survivors tend to become isolated and remove themselves from public activities.

In addition to the President's Cancer Panel, OCS works with other organizations to raise awareness of survivorship research. OCS participated in an American Society of Clinical Oncology media event about survivorship and worked with the Centers for Disease Control

and Prevention and the Lance Armstrong Foundation to champion the importance of cancer survivorship as a public health issue.

http://deainfo.nci.nih.gov/ADVISORY/pcp/pcp03-04rpt/Survivorship.pdf

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Meyer T, Kuhn J, Campbell B, Marbella A, Myers K, Layde P. Speech intelligibility and quality of life in head and neck cancer survivors. *Laryngoscope*, November 2004; 114(11):1977-1981.

Special Needs of Long-Term Cancer Survivors are Focus of New Research

Important new research is underway to address the special needs and health concerns of long-term cancer survivors, as more cancer patients are now able to live for many years after successful treatments.

Once almost uniformly fatal, cancer has become a chronic illness for many and, for a growing number, a curable disease. There are an estimated 9.8 million cancer survivors in the United States today, and an impressive 14 percent of these individuals were originally diagnosed over 20 years ago. While cancer survivors are living longer, we still have limited knowledge and many questions about the health status, functioning, and quality of life for most patients who are post-treatment.

Research projects, coordinated under NCI's Long-Term Cancer Survivors Research initiative, are investigating the full range of issues that affect cancer survivorship—including the physiological, psychological, social, behavioral, and economic impacts of cancer and its treatment, including:

- Long-delayed, potentially life-threatening health effects, such as heart failure resulting from cardiac damage caused by some cancer treatments. Such health effects emphasize the need for extended follow-up
- Other disease- and treatment-related effects—e.g., fatigue, sexual dysfunction, cognitive impairment, neuropathies—that can persist and worsen over time
- Ongoing non-medical burdens of cancer, including treatment costs, and decreased length and quality of survival
- Early identification of, and interventions for reducing, adverse treatment and disease outcomes among long-term survivors

These projects are focusing on the specific questions that may affect long-term cancer survivors to a greater degree than those who are less than five years beyond diagnosis or those with no history of cancer. Some of the studies funded in Fiscal Year 2004 focused on: psychosocial impact of cancer-related female infertility; exercise and fitness in childhood cancer survivors; enhancing wellness in older survivors; and possible Web-based interventions for cancer survivors.

The Long-Term Cancer Survivors Research initiative responds directly to recent Institute of Medicine reports on cancer survivorship, as well the priorities of the President's Cancer Panel. This research is funded in partnership with the National Institute on Aging and the Centers for Disease Control and Prevention.

Follow-Up Guidelines for Childhood Cancer Survivors: First Step to Understanding Late Effects of Curative Treatments for All Ages

Today, treatments for childhood cancers are increasingly effective. As a result, greater numbers of children are surviving cancer. In fact, 75 percent of children diagnosed with cancer are still alive ten years after their initial diagnosis. Yet researchers have noted that the treatments used to cure childhood cancers are not always harmless in the long run. Over time, long-term survivors are at greater risk of developing second cancers as well as of experiencing organ dysfunction, reduced growth and development, and decreased fertility because of the curative treatments they received long ago. These diseases are considered late effects of treating the earlier cancer.

As more children are surviving cancer and living into adulthood, there is an increasing need for clinical practice guidelines to direct the long-term follow-up care for these individuals. In 2004, the Children's Oncology Group, which evolved from the merger of various pediatric cooperative clinical trials groups, released the *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers*. These guidelines are risk-based, exposure-related clinical practice guidelines for screening and managing the late health effects resulting from cancer treatment. The guidelines are intended to standardize and enhance follow-up care for childhood cancer survivors throughout their lives by providing practical clinical recommendations for doctors in a variety of health care settings.

To learn more about the long-term effects of cancer and therapy in childhood cancer survivors, NCI created the Childhood Cancer Survivor Study (CCSS)—a major component of NCI's survivorship research efforts. The CCSS is studying a group of more than 20,000 cancer survivors—originally diagnosed between 1970 and 1986—who have survived for five or more years after a diagnosis of cancer. The study also includes 4,000 siblings of survivors who serve as a comparison group. The knowledge gained from this study may be useful in designing future treatment protocols and intervention strategies that increase survival and minimize harmful health effects. The CCSS is also focused on educating survivors about the potential impacts of cancer diagnosis and treatment on their health, and provides follow-up care through programs aimed at preventing and detecting late effects of cancer treatment.

Data from the CCSS are already providing valuable insights about the potential health consequences that childhood cancer survivors may experience over time. In many cases, "the CCSS findings have more fully defined the high cost of curing cancer for these long-term survivors," says Barry Anderson, M.D., Ph.D., senior investigator in NCI's Cancer Therapy Evaluation Program and scientific liaison to the CCSS. "Moreover, the findings have highlighted the need to decrease the intensity of treatment—and the potential for more serious and long-lasting side effects from treatment—whenever the disease cure rate is sufficiently high."

CCSS data have also shown that many survivors are likely to have comorbid conditions and that the severity of these illnesses will likely affect both the length and the quality of their lives. Based on this information, CCSS scientists are working to include information about comorbid conditions in patient treatment records to improve quality long-term survival.

Two CCSS research reports published in 2004 illustrate the diverse research questions being addressed through this study. In one report, a group of researchers set out to learn about the type of outpatient medical care received by young adults (mean age 26.8 years) who have survived childhood cancers and to examine the factors associated with limited medical care. The group found that, during a two year period, 87 percent reported general medical contact, 71.4 percent a general physical examination, 41.9 percent a cancer-related visit, and 19.2 percent a visit at a cancer center. In general, survivors were less likely to seek care as they aged or as the time from cancer diagnosis increased. This decrease in health care use occurred at a stage in life when the incidence of many late effects of cancer therapy are increasing. Factors typically associated with lack of health care in the population (for example,

lack of medical insurance) were also associated with limited medical contact in this study population. The researchers advised that because primary care physicians provide health care for most of this growing group, it is important that cancer centers and primary care physicians establish methods to communicate effectively over the lifetime of a survivor.

A second report evaluated and compared psychological outcomes in long-term survivors of childhood brain cancer and their cancer-free siblings. Studying levels of distress and depression, the group found that on the surface, survivors and their siblings experienced levels of distress and depression similar to that of the general population. After accounting for sociodemographic, socioeconomic, and health-status variables, researchers found that survivors are much more likely to suffer distress and depression than their siblings. They surmised that these were not caused by the treatment for childhood brain cancer itself but by limited social functioning perhaps related to the cancer type or treatment.

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NIH State-of-the-Science Conference on Improving End-of-Life Care

With improvements in medical science and health care, the nature of death is changing. Today, people are less likely to die suddenly from injury or infection but are more likely to die slowly in old age or at the end of a life-limiting or chronic illness. As a growing share of the U.S. population ages, it is projected that the number of seriously ill and dying people will increase at the same time as the number of caregivers decreases. This projected shift in demographics—which is already beginning to occur—underscores the need to advance end-of-life research and to determine how the care for people at the end of life can be improved.

In December 2004, the National Institutes of Health (NIH) held a State-of-the-Science Conference on Improving End-of-Life Care. Four NIH institutes and centers, including NCI, served as cosponsors of the conference, which was jointly sponsored by the National Institute of Nursing Research (NINR) and the Office of Medical Applications of Research. The conference was the outgrowth of an earlier report from the Institute of Medicine (IoM) entitled "Approaching Death: Improving Care at the End of Life" that drew attention to this issue. NINR and private foundations responded to issues raised in the IoM report by soliciting research proposals that focused on end-of-life issues.

The conference brought together researchers and practitioners in various aspects of end-of-life care and research in an effort to have them consider:

- What defines the transition to the end of life?
- What outcome variables are important indicators of the quality of the end-of-life experience for the dying person and the surviving loved ones?
- What patient, family, and health care system factors are associated with improved or worsened outcomes?
- What processes and interventions are associated with improved or worsened outcome?
- What are future research directions for improving end-of-life care?

Because research into end-of-life care is a relatively new field, the conference was designed to determine what types of research had already been completed, to identify data that may already be available, and to develop recommendations for further research. Researchers

active in the area presented their work in front of a select panel, and the Agency for Healthcare Research and Quality was enlisted to gather relevant published reports. After the conference, the independent panel made several recommendations for future studies in end-of-life research.

"We can begin by refining and agreeing upon our definitions of 'end of life,' 'palliative care,' and 'hospice'—the terms have been used inconsistently and often interchangeably," says Margaret M. Heitkemper, Ph.D., R.N., F.A.A.N., panel chair and professor and chair of the Department of Biobehavioral Nursing and Health Systems at the University of Washington School of Nursing.

Other recommendations included studying ways to enhance communication among patients, families, and providers; recruiting under-represented populations to future studies; and creating new networks of end-of-life researchers and well-defined cohorts of patients to facilitate coordinated, interdisciplinary, multi-center studies.

State-of-the-Science Conference Statement on Improving End-of-Life Care. National Institutes of Health, December 2004. (http://consensus.nih.gov/2004/2004EndOfLifeCareSOS024html.htm)

Approaching Death: Improving Care at the End of Life. Field MJ and Cassel CK, editors; Committee on Care at the End of Life, Institute of Medicine, January 1997.

Overcoming cancer health disparities is a critical component of each of the research areas described in this Annual Report. Sadly, not all Americans are reaping the benefits of the progress made over the past three decades in cancer research and care. Minorities and other underserved populations variously distinguished by race, ethnicity, gender, age, socioeconomic status, geographic location, occupation, and education bear a far greater cancer burden than the general population. The following programs supported in 2004 highlight NCI's leadership in accelerating the implementation and dissemination of interventions to address cancer health disparities across all populations.

8

Overcoming Cancer Health Disparities

"Body and Soul" Changes African American Eating Habits With Help from Churches

In a recent study, researchers from the University of Michigan, University of North Carolina, Emory University, the American Cancer Society (ACS), and the NCI evaluated the effectiveness of the innovative *Body and Soul* national program, which engages African American churches in partnerships to lead their congregations to adopt more healthful eating habits.

They concluded that a research-based intervention can be adapted, implemented, and have a successful outcome when conducted under real world conditions. The *Body and Soul* intervention—which was delivered by volunteers and lay staff rather than professionally-trained individuals—successfully helped participants increase their fruit and vegetable intake. Evaluating the effectiveness of *Body and Soul* in a real world setting was a key step toward developing a program that can be used on a broader scale in the community.

African Americans are at high risk for many serious and often fatal diseases, including many cancers, high blood pressure, diabetes, heart disease, and stroke. Research shows that a diet rich in fruits and vegetables lowers the risk for these illnesses. On average, African Americans eat only about three servings a day. The program encourages eating five to nine servings of fruits and vegetables a day for better health as part of an active lifestyle.

The Body and Soul program was constructed from two previous NCI-funded research efforts: *Black Churches United for Better Health* and *Eat for Life*. It also expands on NCI's long-running "5 A Day for Better Health" initiative, which for years has encouraged increased consumption of fruits and vegetables.

"We looked at the methods of each of these 5-year programs and found that we could adopt and adapt research designs to 'real world' conditions," says Alexis Williams, M.P.H., CHES, with NCI's Office of Education and Special Initiatives (OESI). "What's more, we are using 'lay staff' in *Body and Soul*, as opposed to the professionals used in the original research studies. This means that the work can be replicated broadly with only limited personnel costs."

Body and Soul began as a collaborative effort among two research universities, the ACS, and the NCI. Churches that participate in the program make a serious commitment to fostering change. They serve fruits and vegetables after services instead of pastries. They also sponsor health education classes, food preparation demonstrations and taste tests,

organize tours of food markets, schedule guest speakers, and devote sermons to health issues. Churches plan and organize their programs using NCI's *Body and Soul* program guide.

Fifteen churches participated in the evaluation study. Participants from eight churches received the intervention while participants in the remaining seven churches were the study controls. A total of 1,022 people were recruited across the 15 churches. The participants were asked to complete questionnaires about their fruit and vegetable consumption at the beginning of the study and again after six months. The investigators also measured the participants' fat intake. At six months, fruit and vegetable intake was considerably greater among those who were exposed to intervention efforts than among the control participants. The investigators also observed that fat intake, motivation to eat fruits and vegetables, social support, and intention to eat fruit and vegetables improved with the intervention.

Body and Soul broadened its reach to become a national program in 2004. To raise awareness of the program, NCI conducted outreach with national African American religious organizations and leaders, including the National Black Catholic Conference and the Progressive National Baptist Convention, which passed a resolution to adopt *Body and Soul* for its entire network of 2,500 member churches.

"We know that this program can spark behavior change and increase fruit and vegetable consumption," says Williams. "It is a powerful grassroots approach to closing the health disparities gap for African Americans."

The program has achieved considerable media attention with articles in 13 African American newspapers and in *Jet* magazine. NCI has also engaged gospel recording star Vickie Winans as a national spokesperson for the program. Radio interviews and ads featuring Ms. Winans have resulted in increased requests for the program materials.

In 2005 and 2006, the program is focusing on determining effective methods of reaching African American churches through the NCI's Cancer Information Service (CIS) and national and community-based partners.

Resnicow K, Campbell M, Carr C, McCarty F, Wang T, Periasamy S, Rahotep S, Doyle C, Williams A, Stables G. Body and Soul. A dietary intervention conducted through African American churches. *American Journal of Preventive Medicine*, August 2004; 27(2):97-105.

NCI Supports Radiation Treatment Studies in Medically Underserved Communities

NCI's new Cancer Disparities Research Partnership Program (CDRP) is helping community hospitals and doctors that serve a disproportionate number of minority populations that experience cancer-related health disparities in order to develop stable, long-term radiation oncology clinical research programs and to increase participation of minority patients in clinical trials for new radiation treatments for cancer. The CDRP also helps local clinicians guide their patients through the process of diagnosis and treatment. The long-term goal of this program is to better understand the causes of cancer health disparities and to develop effective approaches to reduce these disparities.

CDRP was created in response to the bleak fact that one in eight Americans —for reasons of economics or location—do not have local access to modern medical care or the opportunity to participate in clinical trials.

Community-based hospitals serving minority populations have not traditionally been involved in NCI-sponsored cancer research. Therefore, the first goal of the CDRP program is to provide resources for the cooperative planning, development, and conduct of radiation oncology clinical research trials and related health services in health care institutions that care for large populations of Hispanic, Native American, Latino, African American, rural, and inner-city people—many of whom live below the poverty line.

The program is growing. Two hospitals began receiving funds for partnerships in fiscal year 2003 and four more institutions were added in fiscal year 2004. CDRP covers a variety of underserved, ethnic, and low-socioeconomic populations that receive care in community hospitals in Laredo, Texas; Rapid City, South Dakota; McKeesport, Pennsylvania; Pascagoula, Mississippi; Wilmington, North Carolina; and Inglewood, California.

One of the funded sites, the Rapid City Regional Hospital (RCRH), serves all of western South Dakota and parts of adjacent states, including three large Indian reservations. As many as 350,000 people rely on this hospital for care. Ten years of data collected at RCRH indicate that Native Americans in this region are usually diagnosed with advanced stages

of cancer when they initially seek medical care—and have higher cancer mortality rates—than do non-Native Americans in the same region. The CDRP program at RCRH is focusing on lowering cancer mortality rates for the Native American population it serves.

With CDRP funding, the hospital is working to document the major factors responsible for cancer-related health disparities in its Native American population; determine whether shorter, but equally effective, treatment courses will improve the acceptance and completion rates for radiotherapy; and explore whether there is a genetic basis for the observations and reports that Native Americans experience greater toxicity from radiation treatments. Because many Native Americans in this community must travel more than 100 miles to undergo cancer treatment at the hospital, the time required for treatment can be a considerable barrier.

Each participating hospital in the CDRP partners with one or more NCI-designated Comprehensive Cancer Centers and is linked to those centers by TELESYNERGY®, a telemedicine system capable of transmitting a wide variety of diagnostic-quality images, including radiology and pathology images. "We provide sophisticated telemedicine systems to the community hospital and their experienced cancer center partners to support and advance the mentoring process, provide clinical research advice and guidance, and import continuing educational activities—despite the community hospitals' geographic isolation," says Frank Govern, Ph.D., NCI's director of CDRP and chief of Oncology Outreach.

"The community hospitals were new to clinical research and required a start-up period to build research infrastructure and capacity and are now actively enrolling minority populations onto clinical trials," Govern notes. "We look forward to the programs reporting their study results over the coming years."

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http://www3.cancer.gov/rrp/CDRP/

Petereit D, Rogers D, Govern F, Coleman N, Osburn C, Howard S, Kaur J, Burhansstipanov L, Fowler C, Chappell R, Mehta M. Increasing access to clinical cancer trials and emerging technologies for minority populations: The Native American Project. *Journal of Clinical Oncology*, November 15, 2004; 22(22):4452-4455.

Patient Navigator Program: Assisting Disadvantaged Patients

NCI's Patient Navigator Program (PNP), a component of NCI's Cancer Disparities Research Partnership Program (CDRP), is addressing the unequal patterns of access to standard cancer care in the United States. The PNP is focused on developing interventions to reduce the delivery time of standard cancer services, cancer diagnosis, and treatment in medically underserved and disadvantaged populations. Within the next decade, these interventions—innovative methods for overcoming the multiple barriers impeding access to care in underserved communities—promise to dramatically reduce cancer health disparities and the burden of cancer by ensuring that knowledge, advancements, and technologies are shared with patients in all communities.

"Patient navigators" help to coordinate services among medical personnel, schedule appointments with caregivers, arrange translation or interpretation services and various forms of financial support, facilitate transportation to and from medical visits, and arrange childcare during diagnosis and treatment appointments. With this assistance, navigators help their patients move through the complexities of the health care system. Navigation spans the period from an abnormal health-related finding, through necessary cancer diagnostic tests, to completion of cancer treatment and follow-up.

Evidence shows that, in addition to unequal access to health care, racial/ethnic minorities and underserved populations do not always receive timely, appropriate advice and care when confronted with a cancer diagnosis. Patient navigators can mean the difference between an underserved individual obtaining and completing critically needed cancer treatment and not getting that care. If navigators get involved early enough after a person has received a cancer diagnosis, they can help steer patients and their families to appropriate care and treatment that could dramatically improve patients' chances of survival. By navigating patients around barriers to quality care, patient navigators actually help ensure that cancer patients are not shortchanged in their options and their care.

PNP pilot projects are currently underway at all CDRP hospitals. At each site, the navigator program is being designed to meet the specific needs of the disadvantaged population it serves. As of this time, close to 900 cancer patients have been navigated through their local health care systems.

At the New Hanover Regional Medical Center in Wilmington, North Carolina, investigators are working to improve treatment outcomes for African Americans. They are developing mechanisms to better communicate with patients, identify and address local factors that inhibit participation in clinical trials, and reduce barriers to facilitate the patients' journeys through the local cancer-care system.

At the Laredo Medical Center in Laredo, Texas, CDRP investigators are focused on improving care for the impoverished Hispanic communities in the region. The greatest needs for these communities are transportation and assistance with financial concerns. One patient navigator is working within this program to help families and patients manage the many issues surrounding cancer diagnosis and care. The navigators also conduct community outreach, promote clinical trials, and link with established local "promotora" programs to train promotoras for help with surveys to evaluate community needs and cancer screening.

At the Daniel Freeman Memorial Hospital in Inglewood, California, investigators are working with disadvantaged, urban Latino and African American populations. They have developed a training manual, as well as patient satisfaction and quality assessment instruments, for use by the navigators in the program. Navigators will help patients comply with treatment, find community resources, and make and help keep appointments.

At the Rapid City Regional Hospital in Rapid City, South Dakota, the focus is on Native Americans. The Native American Patient Navigator Program is designed to assist patients in receiving needed care. Investigators are also collecting data to better understand the barriers to Native Americans receiving care.

Finally, at the Singing River Hospital in Pascagoula, Mississippi, 220 patients diagnosed with cancer have successfully received navigation through the local cancer-care system since the inception of the program. Also, lay health educators work to increase health awareness in the local underserved populations.

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