

# National Cancer Institute

## Division of Cancer Control and Population Sciences 2007 Overview and Highlights



U.S. DEPARTMENT  
OF HEALTH AND  
HUMAN SERVICES

National Institutes  
of Health

Division of Cancer Control  
and Population Sciences

2007 Overview and Highlights



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# FOREWORD

**T**oday, there are nearly 12 million cancer survivors in the United States, an increase from 3 million at the time the National Cancer Act was passed in 1971. Major advances have occurred in the past decade especially. The astounding progress is in part due to the exceptional research conducted and supported by the National Cancer Institute's (NCI) Division of Cancer Control and Population Sciences (DCCPS). DCCPS-funded research has played a pivotal role in moving cutting-edge laboratory and clinical research to individuals with cancer in the communities where they live. I am proud of NCI's investment and accomplishments in cancer control and population sciences research and am especially gratified to join with DCCPS in celebrating its 10-year anniversary.

Since its creation in 1997, DCCPS has led the way at NCI in understanding the causes and distribution of cancer in populations, in supporting the development and delivery of effective interventions, and in monitoring and explaining cancer trends in all segments of the population. By conducting and supporting an integrated program of the highest quality genetic, epidemiologic, behavioral, social, applied, and surveillance cancer research, DCCPS has both generated new knowledge and helped to ensure that the products of cancer control research are effectively applied in all segments of the population. Through innovative research initiatives, strong leadership, and collaboration with valued national partners, as well as the synthesis and dissemination of knowledge, this program has come to stand as the nation's model for cancer control science.

We know it is possible to substantially reduce the number of deaths from cancer by broadening the application of our current knowledge about how to prevent, detect, and treat cancer. As NCI plans for the next decade, our opportunities for progress in these areas are without precedent. DCCPS will continue to play a critical role in accomplishing these strategic priorities by building on the scientific advances it has achieved to date and by developing new initiatives to achieve our shared vision of reducing the burden of cancer for all Americans.

JOHN NIEDERHUBER, M.D.  
DIRECTOR, NATIONAL CANCER INSTITUTE



**DCCPS**

Dr. Robert T. Croyle  
Director

**DCCPS**

Dr. Jon F. Kerner  
Deputy Director for  
Research Dissemination  
& Diffusion

**Office of Cancer  
Survivorship**

Dr. Julia H. Rowland  
Director

**Epidemiology & Genetics  
Research Program**

Dr. Deborah M. Winn  
Associate Director  
(Acting)

**Methods and  
Technologies Branch**

Dr. Mukesh Verma  
Chief

**Modifiable Risk  
Factors Branch**

Dr. Britt Reid  
Chief

**Host Susceptibility Branch**

Dr. Mukesh Verma  
Chief  
(Acting)

**Clinical and  
Translational Branch**

Dr. Deborah M. Winn  
Chief  
(Acting)

**Behavioral Research  
Program**

Dr. Robert T. Croyle  
Associate Director  
(Acting)

**Applied Cancer Screening  
Research Branch**

Dr. Stephen Taplin  
Chief  
(Acting)

**Basic & Biobehavioral  
Research Branch**

Dr. Paige McDonald  
Chief

**Health Communication  
& Informatics  
Research Branch**

Dr. Bradford Hesse  
Chief

**Health Promotion  
Research Branch**

Dr. Linda Nebeling  
Chief

**Tobacco Control Research  
Branch**

Dr. Cathy Backinger  
Chief

# LEADERSHIP AT A GLANCE

## LEADERSHIP AT A GLANCE

The DCCPS senior leadership team is often described as dedicated and innovative. We pride ourselves not only in our dedication to cancer control, but also in our willingness to utilize unconventional ideas and collaborative approaches to accelerate progress in cancer research.



**Applied Research Program**  
Dr. Rachel Ballard-Barbash  
Associate Director



**Surveillance Research Program**  
Dr. Brenda K. Edwards  
Associate Director



**Health Services & Economics Branch**  
Dr. Martin Brown  
Chief



**Cancer Statistics Branch**  
Dave Stinchcomb  
Chief



**Outcomes Research Branch**  
Dr. Steven Clauser  
Chief



**Statistical Research & Applications Branch**  
Dr. Eric "Rocky" Feuer  
Chief



**Risk Factor Monitoring & Methods Branch**  
Dr. Susan Krebs-Smith  
Chief





# LETTER FROM THE DIRECTOR

**2**007 marked the 10-year anniversary of the Division of Cancer Control and Population Sciences (DCCPS) at the National Cancer Institute (NCI). This milestone provides an ideal opportunity to highlight the return on NCI's investment and expectation in cancer control since the creation of DCCPS in 1997. But much work remains to be done. We must also use this juncture to identify new scientific opportunities, challenges, and strategies for success.

This report provides a historical view of cancer control and population sciences research, examples of major scientific advances and accomplishments to date. We hope that readers will better understand the unique role that the division and our many funded investigators have played—and continue to play—in reducing cancer-related risk, incidence, morbidity, and mortality. We also hope that many readers will find this resource useful for identifying potential areas of interest and collaboration.

In selecting which scientific advances to highlight in this report, we worked closely with top experts in the field and focused on specific key criteria: contributions to new discovery or scientific methods, development of new interventions, and translation of science into practice. Because of space limitation, numerous findings and advances could not be included.

Over the past 10 years, DCCPS and its funded investigators have made significant strides in advancing cancer control and population sciences research. Molecular epidemiology, survivorship, and outcomes research are among the fields that have shown remarkable progress as a result of NCI's support. Continued success will hinge on collaborative, transdisciplinary research involving numerous partnerships. A stronger and more diverse national cancer control research program must be created to bring sufficient numbers of outstanding researchers to these partnerships. To accomplish these goals, we will work with our partners to continue to evaluate what has been learned, identify new priorities and strategies, and effectively apply research discoveries to reduce the cancer burden.

I thank the many colleagues, investigators, partners, advisory board and committee members, and NCI leadership for their expertise, dedication, and enthusiasm in helping to fulfill the goals and mission of this division over the past 10 years.

ROBERT T. CROYLE, PH.D.  
DIRECTOR, DIVISION OF CANCER CONTROL AND POPULATION SCIENCES  
NATIONAL CANCER INSTITUTE

# SECTION 1: INTRODUCTION

## THE EVOLUTION OF CANCER CONTROL IN THE 20TH CENTURY

*Cancer control science is the conduct of basic and applied research in the behavioral, social, and population sciences to create or enhance interventions that, independently or in combination with biomedical approaches, reduce cancer risk, incidence, morbidity, and mortality, and improve quality of life.*  
(Cancer Control Program Review Group, 1998—modified).

With the emergence of cancer as a leading cause of disease and death in the industrialized world throughout the 20th century, the definition and role of “cancer control” slowly evolved. The placement of cancer control research at NCI reflects this evolution.



**Barbara K. Rimer, Dr.P.H.**  
DCCPS Director  
1997-2002



**Robert A. Hiatt, M.D., Ph.D.**  
DCCPS Deputy Director  
1998-2003

- 1937** Legislative language first identified cancer control when, with the formation of the NCI (PL 75-224), the Surgeon General was authorized to act through the Institute and the National Cancer Advisory Council to “cooperate with state health agencies in the prevention, control, and eradication of cancer.”
- Mid-1900s** The major focus of cancer control was the dissemination of research discoveries through communications and education. Research in cancer control per se was not yet part of the paradigm.
- 1971** With the enactment of The National Cancer Act (PL 92-218), Congress reaffirmed its support for cancer control and authorized specific dollar amounts for cancer control research.
- 1973** The Division of Cancer Control and Rehabilitation was the first structural unit within the NCI devoted to cancer control.
- 1983** NCI formed the Division of Cancer Prevention and Control.
- 1996** The Cancer Control Program Review Group was convened by the NCI director and the chair of the NCI Board of Scientific Advisors. The board subsequently recommends changes aimed at accelerating reductions in the nation’s cancer burden.
- 1997** On the recommendation of the Cancer Control Program Review Group, the Division of Cancer Control and Population Sciences was established.

\* Photo credit: Jennifer Sauer

## ABOUT THE DIVISION

As NCI's bridge to public health research, practice, and policy, the Division of Cancer Control and Population Sciences (DCCPS) plays a unique role in reducing the burden of cancer in America. An extramural division, DCCPS has lead responsibility at NCI for supporting research in surveillance, epidemiology, health services, behavioral science, and cancer survivorship. The division also plays a central role within the federal

government as a source of expertise and evidence on issues such as the quality of cancer care, the economic burden of cancer, geographic information systems, statistical methods, communication science, tobacco control, and the translation of research into practice. As a result, DCCPS is what many have referred to as a "hybrid" division—one that funds a large portfolio of grants and contracts but that also conducts and disseminates original research to inform public health policy.

## THE EXPECTATION — *From the Cancer Control Review Group Report, 1997*

The Division of Cancer Control and Population Sciences was established in 1997, on the endorsement of the Cancer Control Program Review Group. This group was convened by the NCI director and chair of the NCI Board of Scientific Advisors in 1996. Here are some of their statements regarding the pursuit of research opportunities most likely to accelerate reductions in the nation's cancer burden:

*The new Division of Cancer Control and Population Sciences should create or enhance four major research initiatives in basic behavioral science, primary prevention, screening, and rehabilitation and survivorship. The division should support these initiatives with other cross-cutting units in surveillance, biometry, epidemiology, health services, outcomes research, underserved and high-risk populations, communication and informatics, and training.*

*The success of this program will hinge on collaborative, multidisciplinary research involving numerous partnerships. A stronger and more vibrant cancer control research program must be created to bring sufficient numbers of outstanding researchers to these partnerships.*

*Data show that lifestyle and environmental influences are responsible for a majority of the cancer burden. Thus, the Review Group recommends that NCI pursue a vigorous effort to exploit existing and emerging opportunities in behavioral prevention and cancer control.*

*Given what is now known about the natural course of cancer, NCI must make a long-term commitment to develop a more balanced partnership between the biomedical and behavioral/public health paradigms.*

*Research in cancer control must keep pace not only with new knowledge but with changing demographic trends. We must have the capacity to track cancer and the factors that increase risk.*

*The programs in surveillance, epidemiology, and applied research are crucial to the development of a more timely and useful “report card” to inform decision making about where the research gaps and opportunities lie for cancer control.*

*As knowledge and technology change, so must the emphasis of cancer control research.*

## THE INVESTMENT

Over the past 10 years, DCCPS has funded a large and expanding portfolio of grants, contracts, and interagency agreements. The portfolio currently includes more than 900 grants valued at almost \$400 million. A description of the entire portfolio is not possible here, but the breadth of research supported by the division includes surveillance, statistical and measurement methods, epidemiology, geographic information systems, quality of cancer care, health services, behavioral science, cancer survivorship, the economic burden of cancer, communication science, tobacco control, and the science of implementation.

In recent years, DCCPS also spent approximately \$64 million annually on research contracts and collaborative initiatives with other agencies on such research priorities as quality of cancer care, tobacco control, and cancer surveillance. For example, DCCPS is actively involved in NCI's Quality of Cancer Care Initiative, launched in 1999, which is designed to make cancer a working model for quality-of-care research and application. The initiative includes a research plan to improve the state of the science for defining, monitoring, and improving the quality of cancer care. The NCI Quality of Cancer Care Initiative reports regularly to the NCI National Cancer Advisory Board



and Board of Scientific Advisors and to the National Cancer Policy Forum of the Institute of Medicine. We also maintain close coordination and collaboration with the Agency for Healthcare Research and Quality (AHRQ). An example of a key set of DCCPS contracts is the Surveillance, Epidemiology, and End Results (SEER) Program, the nation's authoritative source of cancer incidence and survival data from population-based cancer registries covering approximately 26% of the U.S. population.

## **LEVERAGING RESOURCES THROUGH PARTNERSHIPS**

One of the primary recommendations of the Cancer Control Program Review Group was for DCCPS to “conduct collaborative, multidisciplinary research involving numerous partnerships.” In response, the division not only relies on the varied and complex expertise and backgrounds of its own scientific staff but also works closely with other National Institutes of Health (NIH) institutes, Department of Health and Human Services agencies, and many nongovernmental organizations—all with their own purposes and objectives and all deeply committed to cancer control. Careful priority setting, planning, coordination, and evaluation ensure that our efforts complement and capitalize on the efforts of other research funding organizations.

DCCPS builds bridges across NCI by fostering collaborative initiatives with other programs, such as NCI-designated Cancer Centers, The NCI Community Cancer Center Program, clinical trials, and Community Clinical Oncology Programs (CCOPs). Recognizing that the “silo approach” to research substantially impedes progress in cancer research, the division also emphasizes and promotes transdisciplinary team science, stretching across multiple disciplines and levels of analysis. By working collaboratively and innovatively, DCCPS-funded investigators and partners can exponentially accelerate progress in the fight against cancer.

## **THIS REPORT**

Throughout this report, we describe and illustrate how DCCPS has optimized the nation's investment and met high expectations over the past 10 years. We highlight some of the most exciting scientific advances in each of our major research areas and describe how these advances have impacted the lives of Americans in the communities where they live.

Perhaps most importantly, we hope to relay how what we have already learned, along with what we will learn through continued cancer control research, can be translated to substantive, near-term actions and real hope for individuals with cancer.

*The Committee sees an important role for NCI in bridging of the gap between research and general medical application. Once the effectiveness of these findings can be demonstrated—to the satisfaction of the scientific community—these results or techniques should be expeditiously communicated to the medical practitioner.*

*The NCI should develop an aggressive and coordinated program to demonstrate the application of recent research discoveries as rapidly as possible, using whatever community resources are available, and communicate these findings to practitioners where these findings can be applied.*

*U.S. Congress (House Report  
No. 92-659, p. 24)*

**I**n addition to the nearly 1,000 valued investigators whose research DCCPS funds, we extend our thanks to our many collaborators and partners.

ABC World News Tonight

Agency for Healthcare Research and Quality (AHRQ)

American Association for Cancer Research (AACR)

American Cancer Society (ACS)

American College of Epidemiology (ACE)

American College of Obstetricians and Gynecologists (ACOG)

American College of Radiology (ACR)

American College of Surgeons (ACoS)

American Joint Committee on Cancer (AJCC)

Commission on Cancer (CoC)

American Legacy Foundation

American Medical Association (AMA)

American Society of Clinical Oncology (ASCO)

C-Change

CancerCare

Centers for Disease Control and Prevention (CDC)

Centers for Medicare & Medicaid Services (CMS)

Department of Veterans Affairs (VA)

Fogarty International Center

Food and Drug Administration (FDA)

Health Research and Services Administration (HRSA)

Indian Health Service (IHS)

Lance Armstrong Foundation (LAF)

National Cancer Registrars Association (NCRA)  
National Heart, Lung, and Blood Institute (NHLBI)  
National Human Genome Research Institute (NHGRI)  
National Institute on Aging (NIA)  
National Institute on Alcohol Abuse and Alcoholism (NIAAA)  
National Institute of Child Health and Human Development (NICHD)  
National Institute of Environmental Health Sciences (NIEHS)  
National Institute on Drug Abuse (NIDA)  
National Institute of General Medical Sciences (NIGMS)  
National Library of Medicine (NLM)  
National Institute of Mental Health (NIMH)  
National Quality Forum (NQF)  
North American Association of Central Cancer Registries (NAACCR)  
Office of Behavioral and Social Sciences Research (OBSSR)  
President's Cancer Panel (PCP)  
Produce for Better Health Foundation (PBH)  
Psychoneuroimmunology Research Society (PNIRS)  
Robert Wood Johnson Foundation (RWJF)  
Society of Behavioral Medicine (SBM)  
Society of Gynecologic Oncologists (SGO)  
Substance Abuse and Mental Health Services Administration (SAMHSA)  
U.S. Census Bureau  
U.S. Department of Agriculture (USDA)  
World Health Organization (WHO)

# SECTION 2: UNDERSTANDING PERSONAL SUSCEPTIBILITY TO CANCER

## MEETING THE CHALLENGE

**E**pidemiology is the science that studies the distribution and determinants of diseases in human populations. Cancer epidemiologists study the effect of environmental and personal susceptibility factors on the risk of cancer and second primary cancers, recurrence, and survival after a cancer diagnosis. Together with basic science findings, the results of epidemiology studies form the basis for making determinations about causes of cancer. Cancer epidemiology also helps to identify opportunities or targets for preventing cancer, and inform clinical practice and public policy and action.

The mission of the Epidemiology and Genetics Research Program (EGRP) in DCCPS is to increase the current understanding of the determinants of cancer and cancer-related outcomes in human populations. Determinants of cancer occurrence and health outcomes include behavioral, environmental, infectious, medical, and sociocultural factors; life events and experiences that have an impact on health; as well as genetic factors and other personal susceptibility factors. The challenge for EGRP is to continue to develop the knowledge base of epidemiologic research by encouraging and funding studies to investigate multiple environmental and genetic factors in human populations with the objective of elucidating the etiology of cancer. Discoveries in epidemiology also generate important hypotheses that can be tested in experimental studies in lower animals and humans. EGRP is the largest funder of etiologic cancer epidemiology grants nationally and worldwide, with support provided to U.S. and international scientists.







## SCIENTIFIC ACCOMPLISHMENTS FROM NCI'S INVESTMENT

### NEW EPIDEMIOLOGIC APPROACHES FOR STUDYING CAUSES OF CANCER

**T**he etiology of most cancers is multifactorial, and there has long been evidence to suggest that both genetic and environmental factors contribute to the development of cancer in human populations. It appears that multiple genetic factors, each with a small effect, may be involved; in addition, heritable factors, not just those involving changes in DNA sequence (i.e., epigenetic factors), may play an important role. Over the past decade, cancer epidemiology investigators have taken increasing advantage of new technologies to better understand how one or more factors may modify and interact with each other to lead to the development of cancer. The mapping of the human genome and advances in molecular genetics technology have made it possible to study more effectively the underlying biologic and genetic mechanisms of cancer. The scientific discoveries from genetic cancer epidemiology are critical to NCI's goals because they inform basic biology;

improve cancer risk assessment; lead to improved prevention, diagnosis, and treatment of cancer; enhance quality of life; and reduce morbidity and mortality after a cancer diagnosis.

Many resources are integral to conducting sound cancer genetic epidemiology research, including sophisticated technologic resources and tools, infrastructures for collaboration, robust study design, and well-trained investigators. The Methods and Technologies Branch (MTB) of EGRP focuses on the development of methods to address epidemiologic data collection, study design, and statistical analysis and to modify technologic approaches developed in the context of other research endeavors for use as biomarkers and methods to understand cancer susceptibility.

### BOTH GENES AND THE ENVIRONMENT CONTRIBUTE TO CANCER RISK

#### Challenge

Until recently it was difficult to understand gene-environment interactions and the influence of multiple genetic factors because of the large numbers of participants needed to conduct appropriate studies and the sophisticated methods needed to identify genetic factors. Until the mid-2000s, the primary approach to





understanding the role of genetic factors in the etiology of cancer was through candidate genes. With this approach, epidemiologists selected genes, or increasingly, gene families, on the basis of what was known about the function of the gene and known or suspected risk factors. Most cancer epidemiology candidate gene studies had not been large enough to provide sufficiently accurate data, and there had been little consistency of findings across studies.

### Response

DCCPS addressed these challenges in a variety of ways. The division worked to establish the research infrastructure needed to improve understanding of the role of genetic factors. It did this by establishing effective partnerships, particularly with NCI's intramural Division of Cancer Epidemiology and Genetics (DCEG), to foster intramural-extramural collaborations, and with genomicists to facilitate the applications of advanced genomic technologies into epidemiologic studies. The division also supported a wide range of groundbreaking research culminating in genome-wide association studies that yielded important new information about cancer development.

Statistical power analyses have indicated that large numbers of study participants and biospecimen samples are critical for obtaining highly informative results from



of studies of genetic and environmental influences on cancer risk. DCCPS and DCEG built capacity by facilitating and funding the development of approximately 30 consortia that allow for large-scale collaborations. These consortia include ones based on cancer organ sites as well as those based on traditional epidemiology designs (e.g., cohort, case-control, case series, and family-based). These consortia enable investigators to expand the size of their study populations, share data and resources, and benefit from each other's expertise.

By networking genomicists and epidemiologists with each other and fostering and supporting sophisticated grant applications that included teams of these investigators working together, DCCPS was able to ensure that state-of-the-art technology could be quickly incorporated into epidemiologic studies in which either a candidate gene or genome-wide approach or both was used to discover genetic factors involved in susceptibility

to cancer. Compared with the candidate gene approach, genome-wide association studies offer the benefit of a comprehensive scan of the entire human genome in an unbiased fashion. In these studies, DNA biospecimens from thousands of people with and without cancer who are participants in cancer epidemiology studies are compared using hundreds of thousands of single nucleotide polymorphism (SNP) markers located throughout the genome. SNPs are minute variations in DNA that may or may not change the function of the gene. The sum of many slightly altered genes may significantly increase the risk of a specific disease, including cancer. Technologies for scanning the genome have become much less costly, and the decreasing costs of genome-wide association studies have increased their feasibility in large-scale epidemiology studies.

### Progress

By pooling data and samples from many studies, investigators in the research consortia were able to conduct large-scale studies with the candidate gene approach as well as with genome-wide association studies, providing new and more accurate estimates of genetic effects.

Beginning in 2007, the findings from a number of genome-wide association studies, supported by DCCPS, DCEG, and other organizations were published with many interesting and surprising results. For example, a number of investigators have reported findings that suggest that areas on the long arm of chromosome 8, a region known as 8q24, are linked to cancers of the breast, prostate, and colon. Within that region, certain areas seem to be specific for one or the other of these cancers; also, cancers of the colon and prostate share an area. Of even more interest, is that there are no genes located in this area, suggesting that heretofore unknown factors are playing a role in cancer etiology. It will be fascinating to learn what these factors are. Moreover, because some of these risk variants are more common in certain racial/ethnic groups, these findings may help to explain at least some of the disparities in cancer incidence by race/ethnicity. Many genome-wide association studies of other cancers are being published.

There remain many challenges. The results of research now nearing completion seem to confirm some of these findings, but data from genome-wide

**T**he Division of Cancer Epidemiology and Genetics (DCEG) at NCI conducts population and multidisciplinary research to discover the genetic and environmental determinants of cancer and new approaches to cancer prevention. The DCCPS Epidemiology and Genetics Research Program (EGRP) facilitates movement of discoveries about the determinants of cancer and cancer-related health outcomes after cancer into clinical and public health practice. DCEG and EGRP join together on large-scale collaborations, the Cohort Consortium, in order to have sufficient data and biospecimens to study gene-gene and gene-environment interactions in the etiology of cancer. DCEG and DCCPS researchers foster communications, promote collaborative projects, and identify common challenges and solutions. This collaboration provides a coordinated, interdisciplinary approach to tackling important scientific questions, economies of scale, opportunities to quicken the pace of research, and a collaborative network of investigators.

association studies are not yet available for most cancers. Considerable work will still be needed to validate these findings, better localize the areas of the genome that may be responsible for the findings, understand environmental factors that may influence the genetic predisposition, and better understand the underlying biology.

These findings are an important step toward the ability to identify individuals who might benefit from risk factor counseling or preventive measures or who should be screened for cancer more aggressively because of their genetic risk profile.

#### EPIGENETICS: A NEW WAY OF UNDERSTANDING CANCER RISK AND SUSCEPTIBILITY

##### Challenge

Genetic information in the genome provides the blueprint for the manufacture of all the proteins necessary to create a living organism. However, this blueprint does not provide details about how, where, and when the genetic information will be used. To determine these details, it is necessary to study mechanisms that involve mitotically heritable (i.e., can be passed down to one's offspring) changes in DNA other than changes in the sequence of nucleotides, the building blocks of DNA. This study is epigenetics, which represents a new frontier in cancer research. Epigenetic changes have great functional importance, as they regulate gene expression. Epigenetics involves chromatin remodeling, histone acetylation and deacetylation, and DNA methylation in the promoter region. Chromatin is composed of DNA and the proteins, including histones, that help give chromosomes their tightly

coiled physical structure and shape. The chemical changes known as acetylation and deacetylation influence that shape and structure and can influence gene regulation, DNA repair, and other biologic processes. Methyl chemical groups can bind to DNA at the cytidine residue. Abnormal methylation of tumor suppressor genes, oncogenes, and other types of methylation patterns may contribute to results in development of cancer.

There were many challenges in the fields of cancer epidemiology and epigenetics research: determining the influence of physical, chemical, and infectious agents and behavioral factors on the types and levels of epigenetic changes in human populations; determining the role of epigenetic changes in the risk of cancer in human populations; identifying genetic, environmental, and host susceptibility factors that modify the risk of cancer associated with epigenetic changes; investigating whether epigenetic markers identified in cohort and case-control studies will be sensitive and specific enough to help in identifying high-risk populations; and determining whether epigenetic factors can help explain disparities in cancer incidence.

An important distinction between genetic and epigenetic changes in cancer is that therapeutic interventions may reverse epigenetic changes more easily than genetic changes. Understanding the epigenetic alterations in precancerous lesions that lead to cancer development was critical, as this knowledge could be applied to risk assessment and early detection efforts and could also provide molecular targets for chemoprevention interventions.



### Response

The inclusion of epigenetic factors in research on the etiology of cancers is a logical next step in the elucidation of genetic and environmental influences. EGRP led the way by stimulating the extramural epidemiologic community to address this relatively new area of emphasis through a series of program announcements that called for population-based studies to evaluate determinants of methylation patterns, risks of cancer associated with DNA methylation, and markers and modifiers of cancer risk.

In addition, a DCCPS research resource that focuses on colon cancer, the Colon Cancer Family Registry, is playing a major role in unraveling the role of epigenetics in the etiology of colon cancer.

### Progress

Research showed that a large number of cancer genes carry a high level of methylation in a normally unmethylated promoter. The epigenetics of colorectal cancer has been studied in detail. Colorectal cancer arises as a consequence of both genetic and epigenetic alterations, including promoter CpG island hypermethylation. These are areas that harbor genes potentially involved in the suppression of cancer that can have their suppressive action stopped (or

“silenced”) by methylation of the DNA in those areas. A subset of colorectal tumors has been described to have an unusually high number of these hypermethylated CpG islands, leading to the definition of a distinct phenotype, referred to as CpG Island Methylator Phenotype (CIMP).

Investigators used colorectal cancer samples collected through the Cooperative Family Registry for Colorectal Cancer Studies (Colon CFR), an NCI-supported consortium established to promote collaborative and interdisciplinary studies in the genetic epidemiology of colorectal cancer, to identify populations at high risk for colorectal cancer on the basis of CIMP phenotype and microsatellite instability. Research is being conducted to estimate the association between CIMP status and both genetic risk factors (such as somatic mutations in selected genes [e.g., BRAF], germline mutations in the MMR genes, and folate metabolic enzyme polymorphisms) and environmental/lifestyle risk factors (such as smoking history, intake of red meat and alcohol, dietary folate intake, and history of hormone use).

DCCPS-supported investigators are exploring the role of epigenetics in other cancers as well. In one study, researchers are evaluating so-called triple negative breast tumors (tumors that lack expression of HER2/neu, estrogen, and progesterone).



terone receptors) from black women and white women to determine if methylation patterns differ and to evaluate other predictors (epidemiologic and genetic) that may differ in these two populations of women. In another study, investigators found that the silencing of three tumor suppressor genes was associated with a more advanced stage of bladder cancer at diagnosis and survival.

Studies involving environmental and occupational exposure, infectious agents, personal susceptibility factors, and acquired genetic factors may identify populations at high risk for the development of cancer. Epigenetic biomarkers can be used to identify the high-risk population that may benefit from intervention, and epigenetic changes can be used as markers for screening cancer. Therefore, these studies are informative and significant in designing future community-based health initiatives.

## MODIFIABLE RISK FACTORS

Many lifestyle behaviors have been shown to be associated with the development of cancer. The Modifiable Risk Factors Branch (MRFB) of DCCPS develops and coordinates a comprehensive program of extramural epidemiologic population-based research on the etiology of cancer relating to such factors as nutrition, physical activity and energy balance, infectious diseases, and physical and chemical agents.

In addition to lifestyle factors, exposure to some environmental factors, such as ultraviolet radiation, physical and chemical agents, and infectious diseases are also associated with cancer risk. Determining



the role of these factors is essential for developing measures to prevent cancer and for informing policy regarding public health programs. In the area of energy balance, MRFB efforts complement the work of the Risk Factor Monitoring and Methods Branch in DCCPS, which fosters research in the monitoring of energy balance in the U.S. population and methods to measure it. These two groups also work with the DCCPS Health Promotion Research Branch, which coordinates research on the behavioral prevention of cancer in the areas of physical activity and energy balance.

## ENERGY BALANCE EMERGES AS A MAJOR POTENTIAL RISK FACTOR IN CANCER ETIOLOGY

### Challenge

Since the mid-1970s, the prevalence of overweight and obesity had increased sharply for both adults and children, and current rates had reached epidemic proportions in the United States. Data from two National Health and Nutrition Examination Surveys showed that among



adults 20-74 years old, the prevalence of obesity increased from 15.0% (in the 1976–1980 survey) to 32.9% (in the 2003–2004 survey).

In 2002, the International Agency for Research on Cancer Prevention report, *Weight Control and Physical Activity*, indicated that avoidance of adult weight gain protected against cancers of the colon, uterus, and kidney; post-menopausal breast cancer; and adenocarcinoma of the esophagus. The report estimated that, for many of these cancers, 25% to 34% may be attributable to the combined effect of increased body weight and inadequate physical activity. Also noted was an independent association between physical activity and reduced risk of cancers of the colon and breast. In addition, the findings of a 2003 study of 900,000 men and women who were followed for 16 years demonstrated that overweight and obesity may have accounted for 20% of all cancer-related deaths in women and for 14% of all cancer-related deaths in men.

These findings caused great concern for how behaviors involving body weight, physical activity, and diet may affect the development of cancer as well as prognosis for cancer survivors. Although cancer epidemiologists had studied diet, nutrient intake, obesity, and physical activity as independent potential risk factors for cancer, until 1997 little attention had been devoted to the combined effects of body composition, weight, physical activ-

ity, and diet on the key physiologic processes involved with cancer.

### Response

In response to this challenge, DCCPS developed two initiatives. First, four centers and one coordinating center were funded as part of the Transdisciplinary Research on Energetics and Cancer (TREC) initiative in 2005.

This initiative is designed to foster collaboration among transdisciplinary teams of scientists, with the goal of accelerating progress toward reducing cancer incidence, morbidity, and mortality associated with obesity, low levels of physical activity, and poor diet. The initiative also provides training opportunities for new and established scientists who can carry out integrative research on energetics and energy balance. The TREC project complements other NCI energy balance research endeavors and the efforts of the NIH Obesity Task Force.



DCCPS also initiated the program announcement, “Ancillary Studies of Energy Balance and Cancer-Related Exploration in Human Studies,” inviting new research applications as well as competitive supplements to existing NCI-funded grants that explored relationships between energy balance and cancer risk and prognosis. The program announcement requested applications proposing new hypotheses within existing studies



as well as encouraging collaborations among scientists working in many disciplines.

One of the greatest challenges in this area of research is the paucity of adequate tools to measure energy balance. To help address this problem, DCCPS coordinates the NIH-wide effort, Improved Measures of Diet and Physical Activity for the Genes and Environment Initiative. This program is designed to promote substantive work to refine or improve the assessment of usual diet and physical activity. Specifically, applications are solicited for projects to develop new technology or to adapt existing technologies (such as sensors, scanning and/or measurement devices, imaging techniques, wireless technologies, and bioinformatics tools and solutions) for assessment of dietary intake and physical activity.

### Progress

As these initiatives mature, evidence from DCCPS-supported research continues to support that energy balance, defined as the integrated effects of diet, physical activity, and genetics on growth and body weight over the life course, plays a far more important role in the risk of cancer than the individual effect of any one factor. The association between energy balance and cancer appears to exist in both men and women, in multiple racial/ethnic groups, even when controlling for other potential risk factors.

In the NCI report *Nation's Investment in Cancer Research* (Fiscal Year 2007), targeting specific public health needs is one of three key components that includes recognition of the importance of research in the area of energy balance, diet, exercise, and weight management. Therefore, there is a need to continue investigations of the potential role of energy balance and energetics in the development of cancer and to define the factors that affect energy balance and related mechanisms influencing cancer risk, prognosis, and quality of life.

### VITAMIN D MAY PROTECT AGAINST CANCER

#### Challenge

Since the 1930s, it had been recognized that cancer-related mortality was higher among people who live in colder climates with less exposure to sunlight. The results of studies in the late 1980s and early 1990s confirmed that increased blood levels of vitamin D had a protective effect against cancer of the colon, prostate, breast, and ovary. However, recommendations for vitamin D to prevent cancer





were complicated by many facts. First, vitamin D can be produced in the human skin in response to ultraviolet rays from the sun, but sunlight exposure increases the risk of skin cancer. Vitamin D can also be obtained through the diet, and it is found in dairy products and fish as well as other fortified foods and dietary supplements. Many research questions surrounding recommendations existed, especially when genetic variation and differences in skin color as well as interactions of vitamin D with other nutrients were considered.

### Response

Several investigators funded by EGRP studied the relationship between cancer risk and blood levels of vitamin D, as well as dietary intake and consumption of dietary supplements containing vitamin D. To address this question, investigators used data from two large cohort studies: the Nurses Health Study, in which more than 122,000 women had been followed since 1976, and the Health Professionals Follow-Up Study, in which more than 51,000 men had been followed since 1986. The researchers found data supporting a protective effect of vitamin D against cancer risk.

Most recently, the conference “Vitamin D and Cancer: Current Dilemmas/Future Needs” was held in May 2007. Sponsored

by the Division of Cancer Prevention, DCCPS, DCEG, and the Office of Dietary Supplements, the conference was designed to critically evaluate the scientific evidence related to vitamin D and cancer risk, to identify gaps in knowledge, and to determine the research needed to establish science-based recommendations for vitamin D intake/exposure for cancer prevention. One recommendation to emerge from this conference was to leverage past and current expenditures by performing additional analysis of epidemiologic studies, especially those with stored biologic samples.

Lastly, DCCPS funded a cohort consortium pooling project through nested case-control studies to investigate the relationship between blood levels of vitamin D and the risk of six types of cancer: pancreatic, ovarian, upper gastrointestinal, endometrial, renal, and lymphoma. This project will provide a greater opportunity to combine data from different studies to allow for better ability to draw conclusions about the relationship of vitamin D levels and cancer risk.

### Progress

Studies funded by EGRP demonstrated many important findings. For example, low blood levels of vitamin D were shown to be associated with a substantially higher risk of colon and breast



cancers and possibly with other types of cancer as well. In contrast, higher blood levels of vitamin D were associated with a decreased risk of colorectal adenomas, a precursor of cancer, and with better survival rates for individuals with early stage nonsmall cell lung cancer.

Among premenopausal women, the risk of breast cancer was reduced for women who took more than 500 IU of vitamin D daily. Investigators suggested that the association between vitamin D status and the risk of several cancers may vary because of a genetic risk referred to as the Vitamin D Receptor (VDR) genotype. Genetic differences in VDR among populations may account for variation in the impact of diet and lifestyle factors.

#### BREAST CANCER AND THE ENVIRONMENT: FINDINGS IN ADULT WOMEN FOCUSES ATTENTION ON EXPOSURES EARLIER IN LIFE

##### Challenge

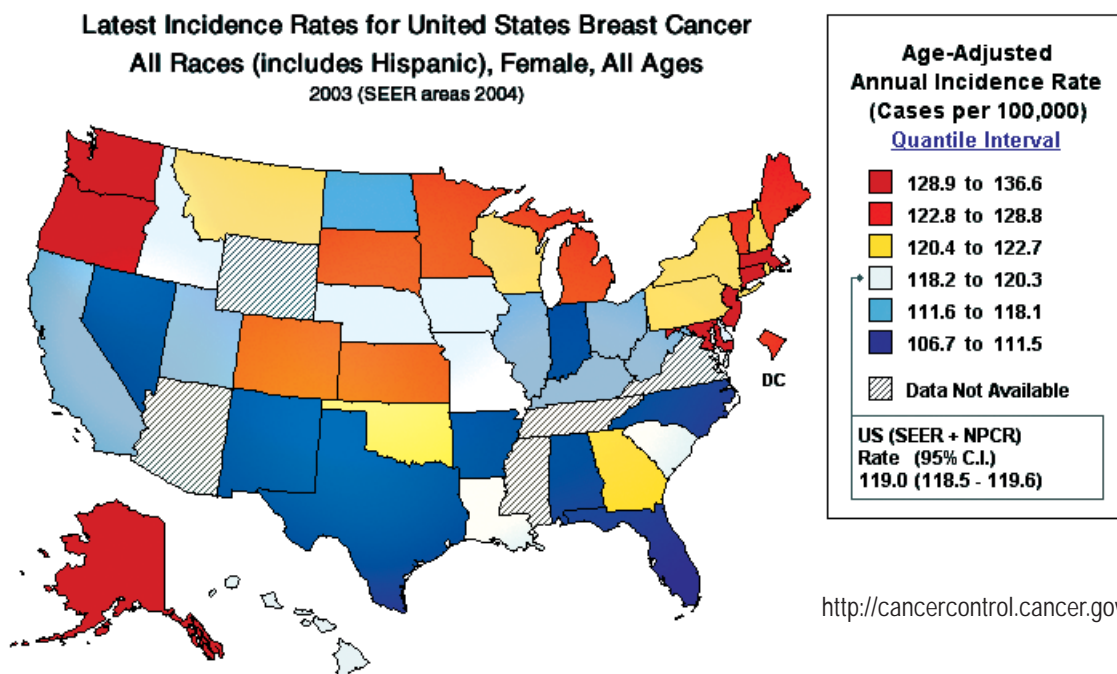
In the 1990s, it was discovered that breast cancer-related mortality rates were higher among white women in the Mid-Atlantic, Northeast, and North Central regions of

the U.S. Although studies suggested that the higher rates of breast cancer were probably due to established risk factors (e.g., age at menarche, age at first pregnancy, obesity), there was still concern that chemical and physical environmental factors, such as pesticides and electromagnetic fields, may be the cause of the increased incidence, especially in the Northeast. Residents in Long Island, NY, were particularly concerned about breast cancer and the environment, and breast cancer advocates from Long Island and other areas, including Marin County, California, sought assistance from their Congressional representatives.

Congressional involvement, the emergent role of breast cancer advocates in the research process, and the research findings themselves have made and continue to make the study of breast cancer and the environment scientifically and socially unique.

##### Response

In response to these concerns, in 1992, the U.S. Congress requested a study on factors that might contribute to the high breast cancer-related mortality rates in



the Northeast and Mid-Atlantic regions. NCI and the National Institute of Environmental Health Sciences (NIEHS) took the lead and funded six studies, known collectively as the Northeast and Mid-Atlantic (NE/MA) Breast Cancer Study. Five of the studies focused on chemical exposures, particularly organochlorines (pesticides including DDT and polychlorinated biphenyls), and one study focused on electromagnetic fields.

While the NE/MA study was ongoing, in 1993, breast cancer advocates in Long Island were successful in petitioning Congress to pass Public Law 103–43, which mandated NCI and NIEHS to support case-control studies to investigate environmental exposures and breast cancer on Long Island and to undertake the development of a geographic information system on Long Island. The Long Island Breast Cancer Study Project (LIBCSP) consists of more than 10 initiatives that include epidemiologic studies, establishment of the Metropolitan New York Registry of Breast Cancer Families, laboratory research, and development of a researcher and public geographic information system. The LIBCSP specifically investigated organochlorines, polycyclic aromatic hydrocarbons, and electromagnetic fields in relation to breast cancer.

### Progress

Findings from the NE/MA study were published in 2001. The results demonstrated no link between DDT, polychlorinated biphenyls, or electromagnetic fields and an increased risk for breast cancer. In addition, the LIBCSP results, most of which were published in 2002, showed no relationship between the organochlorines, electromagnetic fields, and the high incidence of breast cancer on Long

Island. A modest association with polycyclic aromatic hydrocarbons was observed. Pooled data from the other studies also indicated no significant associations between the organochlorines and breast cancer. The largest study did confirm many of the well-known risk factors for breast cancer, such as increasing age and family history.

Since the LIBCSP, a new generation of research on the relationship between breast cancer and environmental factors research has been underway. Funded in 2003, the Breast Cancer and the Environment Research Centers (BCERCs) have taken an innovative approach to studying the environmental causes of breast cancer by focusing on girls rather than adult



women. Because early puberty is a risk factor for breast cancer, there may be a critical window of susceptibility during which time the developing breast is more vulnerable to environmental exposures. The BCERCs are using complimentary animal and epidemiologic studies to evaluate the impact that prepubertal environmental exposures (such as phytoestrogens, phthalates, and diet) have on pubertal development and future breast cancer risk. The project also includes a joint Community Outreach and Translation Core that involves individuals from the community who are advocates concerned about breast cancer risk.

The LIBCSP also marked the beginning of advocates as an integral component of the research on breast cancer and the environment, and it is now commonplace for advocates to serve in a variety of capacities in the research process.





## HUMAN PAPILLOMAVIRUS: PUBLIC HEALTH PROGRESS, BUT SCIENTIFIC CHALLENGES REMAIN

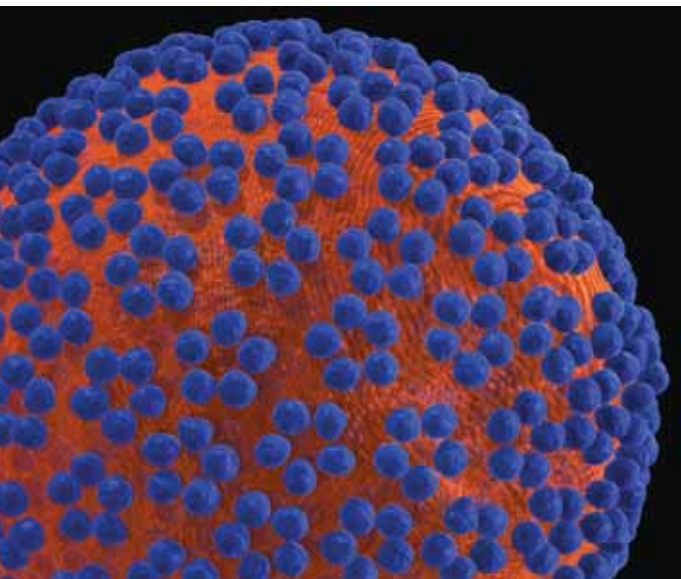
### Challenge

Recognition of the infectious agents that cause cancer is essential for establishing prevention and control measures to reduce the risk of infection with causative agents. NCI-funded research had included studies of many infectious agents, a number of which had been identified as causes of cancer, including *Helicobacter pylori*, human papillomavirus (HPV), Epstein-Barr virus (EBV), hepatitis B and C viruses (HBV and HCV), human immunodeficiency virus (HIV) (an indirect cause), human herpesvirus (HHV-8), and human T-lymphotrophic virus-1 (HTLV-1). Although many of these agents had already been classified as carcinogens prior to 1997, it was clear that although many people became infected with these

agents, cancer subsequently developed in relatively few. Understanding the factors that contribute to the development of cancer in infected individuals was essential for identifying those at highest risk of cancer and those in greatest need of preventive approaches.

### Response

DCCPS has supported several large natural history research projects. EGRP funded a large international (United States, Mexico, and Brazil) prospective study of HPV in men, evaluating 3,000 male subjects every six months for four years, to provide useful information for developing vaccination strategies targeting men, as well as for answering questions relative to the natural history of male HPV infection. It also has cofunded, with other agencies, the Women's Interagency HIV Study, a multicenter cohort study (with enrollment of 2,793 HIV-positive and 975 HIV-negative women) that was funded to investigate the effects of HIV coinfection on HPV and cervical dysplasia. In addition, DCCPS has supported a wide range of studies to provide greater insight into the nature and effects of HPV in populations, including acquisition of the infection, persistence of the infection, development of precursor lesions, and progression to cancer.



### Progress

EGRP-supported research showed that for 70% of women, cervical HPV infection becomes undetectable within two years, even without treatment. Among women with persistent infection, “high-risk” types of HPV is the main risk factor for cervical cancer. DCCPS-supported research found that a number of factors influence persistent infection, including immuno-suppression, HIV status, and certain genotypes involved in the HLA immunologic system.

DCCPS played a role in some of the major developments relating to HPV that occurred in the decade from 1997 to 2007. In June 2006, the first FDA-approved vaccine against HPV, Gardasil, was approved for clinical use in girls and women 9–26 years old, before the onset of sexual activity and acquisition of HPV infection. The vaccine protects against infection with HPV 6, 11, 16, and 18, which most commonly cause cervical cancer. Other prophylactic vaccine candidates are in the pipeline. Various DCCPS-supported principal investigators collaborated with pharmaceutical companies and NCI intramural scientists in the vaccine efforts by developing serologic

assays and in providing longitudinal data as a basis for HPV natural history studies, which is a necessary step in vaccine development. However, as is the case with many other viruses and infectious agents that cause cancer, it is critical to gain a better understanding of which infected individuals will subsequently have cancer.

In studying the association between HPV and cervical lesions, DCCPS investigators found evidence to suggest that squamous metaplasia serves as a biologic event that supports the development of low-grade squamous intraepithelial lesion as well as viral replication, which in turn, results in viral transcription of proteins important in cellular proliferation and the cytoskeletal changes associated with squamous intraepithelial lesion. A report on the high rates of regression of this early lesion influenced two important new guidelines: the American Cancer Society guidelines for when cervical cancer screening should begin and the American Society for Colposcopy and Cervical Pathology guidelines for the management of low-grade squamous intraepithelial lesions in adolescents. The new guidelines will reduce the number of cases that are



overtreated, which is common in the adolescent age group.

In contrast, a study demonstrated that young women could be positive for HPV DNA and yet have normal findings on cytologic analysis and colposcopy. The lack of association between clinical disease and viral persistence at levels detectable by the RNA-DNA hybridization technique suggests that key events must occur in the multistep process of neoplasia before histologic descriptions of dysplasia are seen.

HPV is not the only infectious agent for which cancer epidemiologic advances have been made by DCCPS investigators. However, because of the heavy investment of DCCPS in HPV research and the rapid scientific and public health developments related to HPV, this particular virus will be used as an example of the types of infectious disease research that DCCPS supports and ways in which it makes a difference.

## HOST SUSCEPTIBILITY FACTORS

Many factors contribute to an individual's susceptibility to cancer. Enhanced knowledge of how these factors work alone or in combination to influence a person's risk of cancer is a first step toward the development of individualized approaches to prevention and/or treatment on the basis of such factors as genetics, epigenetics, immunologic and hormonal biologic pathways, race/ethnicity, and sociocultural issues. The DCCPS Host Susceptibility Branch fosters research in these important areas of epidemiologic research.

## RACIAL/ETHNIC DIFFERENCES IN RISK OF CANCER ASSOCIATED WITH SMOKING

### Challenge

Differences in the risk of cancer associated with smoking had been identified among some population subgroups, but little was understood about how risk varied among racial/ethnic groups, why the differences existed, or what mechanisms may help to explain the differences.

### Response

EGRP supported a large number of molecular and genetic epidemiologic investigations in which racial/ethnic variations in risk were studied. These studies took into account tobacco use behaviors, and the results indicated that smoking conferred a greater risk for tobacco-associated cancers in some populations.

### Progress

Studies found that differences in smoking behaviors, diet, and genetic profiles may explain many of the disparities, especially racial/ethnic differences, in the risk of cancer related to smoking. In addition, it was found that the amount of tobacco smoke constituents delivered to a smoker is not just a function of the number of cigarettes smoked, which is the typical measure of convenience used in studies of tobacco and cancer, but also a function of puffing behaviors. (See Section 3, *Cancer Prevention and Control*.)

A multiethnic cohort study of more than 11,000 black individuals, with more than 600 cases of lung cancer, demonstrated that black smokers may be at greater risk for lung cancer than white smokers. The higher levels of tobacco smoke constituents per cigarette smoked found





in black men may be related to differences in puffing behaviors. Other studies on the effect of race/ethnicity showed that lung cancer is more likely to develop in cigarette smokers who are black or Native Hawaiian than smokers who are white, Japanese American, or Latino.

Research indicated that differences in the age at the time of smoking initiation may also be a contributing factor for success in quitting smoking. Age at initiation is itself influenced by many factors. For example, in the Mexican population, the influence of parental smoking was pronounced among the youngest initiators. The results point to the need to address family smoking dynamics in this population in order to develop effective prevention programs tailored to this at-risk age group. Interventions should be tailored according to sex, nativity, and acculturation level, and should target individuals of all ages, not just young people.

Differences in nutrient intake may also be a factor in differences in tobacco-related cancer risks. Investigators found that specific phytochemicals (i.e., quercetin, naringenin, apigenin, isothiocyanates) have a protective effect against lung cancer, indicating a nutritional role in risk for cancer that may vary with variation in consumption of these nutrients across racial/ethnic groups.

Lastly, genetic variation may account for differences in both susceptibility to addiction to nicotine and cancer risk. Studies have suggested associations between several polymorphisms and lung cancer. An XPA polymorphism modulates nucleotide excision repair capacity and is associated with decreased risk for lung cancer, particularly among individuals who have ever smoked. This pattern was statistically significant for white and Mexican individuals but not for black individuals. Function-altering polymorphisms in both the UGT1A7 and UGT1A10 genes were shown to be linked to altered risk for orolaryngeal cancer. Gene variants in five pathways are implicated in the susceptibility to lung and upper aerodigestive tract cancer, either on their own or by interacting with environmental exposures. These five pathways are cell cycle control, DNA repair, folate metabolism, alcohol metabolism, and metabolism of environmental exposures.

#### COMBINED INFLUENCE OF GENETIC HERITAGE AND SOCIOCULTURAL FACTORS HELP EXPLAIN DISPARITIES IN CANCER ETIOLOGY

##### Challenge

As defined by NCI, “cancer health disparities” are differences in the incidence, prevalence, mortality, or burden of cancer and related adverse health conditions that



exist among specific population subgroups in the U.S. The rate of newly diagnosed cancers was highest among black individuals, followed by white and Hispanic individuals, Asian/Pacific Islanders, and American Indians. One focus of cancer epidemiology is to understand the basis for disparities in the risk of cancer.

Studies of migrants had shown that, for many cancers, incidence rates shift to resemble those of the populations already living where migrants have moved to, suggesting an important influence of environmental factors. Yet, many cancers also appeared to “run in families,” suggesting an important influence of genetics. Understanding the genetic versus environmental factors was important because it could help in the development of preventive approaches, the identification of populations that may benefit from screening for cancer, and the elimination of disparities in the burden of disease across racial/ethnic groups.

### Response

Over the last 10 years, DCCPS made important contributions in developing infrastructure and supporting research to understand the interrelationships of racial, ethnic, and cultural identity in cancer incidence disparities. EGRP has increasingly focused on supporting studies that included significant racial/ethnic diversity among study populations. For example, in one cohort study that is recruiting more than 90,000 people in the southern part of the United States, 70% of the study population is of racial/ethnic minority. Another major cohort includes substantial numbers of Japanese American, Native Hawaiian, and black individuals in addition to white individuals. EGRP supported many other investigations that specifically addressed disparities. Additionally, EGRP funded and organized a workshop on the impact of genetic diversity within Latino populations on risk factor associations and cancer. EGRP has also supported and developed the Breast and Colon Cancer Family Registries that have made important contributions with respect to factors



that influence the development of cancer in persons from high-risk families.

### Progress

Research has indicated that some racial/ethnic differences in the incidence of prostate cancer can be explained by genetic factors. Investigators using pooled data from several studies found that the risk of prostate cancer appeared to be similar across various racial/ethnic groups, but the genetic variants associated with higher risk were more common among black men. This finding may help to explain some of the reasons for the high rates of prostate cancer among black men.

A role of common genetic variants—such as those affecting candidate gene function and on chromosome 8q24 and other chromosomes—is also likely to contribute to familial clustering. However, in addition, some cancers may be due to “founder effects,” mutations that occurred in a small population group that were passed down to offspring across generations. Identification of these mutations may help determine the subset of individuals who may benefit from enhanced surveillance, chemoprevention, and/or risk modification strategies.

Despite progress made, the challenges remain significant. During the last 10 years, there has been an improved understanding of the differences in population distributions of genetic variations, founder effects, as well as new methods

for characterizing individuals based on their genetic make-up. Comparisons of different populations categorized according to genetic make-up as well as their cultural, social, and lifestyle characteristics will most likely provide much greater insight into the interrelationship of all of these factors in cancer risk and associated disparities. But more work is needed to continue to build the research infrastructure and support the research that will explain disparities in cancer risk in a more comprehensive way.

### INFLAMMATION IS A COMMON PATHWAY IN CANCER ETIOLOGY

#### Challenge

In the mid-1990s, it was evident that inflammation played a critical role in the development and progression of cancer. Long-standing observations had shown that cancer sometimes developed in sites of scarring and injury. With initial reports of reduced risk of cancer in users of nonsteroidal anti-inflammatory drugs (NSAIDs) came the possibility of a larger role and an opportunity to take advantage of the “natural experiment” to further investigate the issue.

Because inflammation is difficult to measure, one challenge had been to identify surrogates, appropriate questions, and relevant biomarkers. Large-scale epidemiologic studies played a key role in documenting an inverse association between use of aspirin (a first-generation NSAID)



and other NSAIDs and the incidence of particular types of cancers, as well as their preventive action among high-risk healthy individuals and cancer survivors. In addition, because inflammation might occur after a cancer has arisen, prospectively collected data were also of great value, even though information on inflammation had been collected in few such studies.

### Response

EGRP supported numerous studies that were based on the hypothesis that inflammation and inflammatory pathways may play a role in cancer development and prognosis. Of particular interest to EGRP-supported investigators is the role of NSAIDs as potential chemoprevention agents against certain cancers, including colorectal, breast, ovarian, and prostate cancers, melanoma, and hematologic malignancies. In addition, EGRP-funded investigators are attempting to elucidate the relationship between the anti-inflammatory action of NSAIDs (i.e., inhibitors of cyclo-oxygenase [COX] enzymes that produce prostaglandins [PGs]) and the genetic variations that exist in inflammatory pathways (PG/epidermal growth factor receptor [EGFR] pathway) that have been proposed to be involved in carcinogenesis.

### Progress

Whether induced by infection, heightened by host factors such as obesity, or caused by minor repeated injury, inflammation has come to be regarded as a fundamental aspect of carcinogenesis. The results of the most recent studies showed

that genes controlling the inflammatory response and related aspects of innate immunity are related to the risk of the development of lymphomas and other cancers. Inflammation appears to play a role in the development of many forms of cancer, including melanoma, lymphoma, and cancers that arise in the colon, prostate, biliary tract, esophagus, and urinary bladder.

The findings of recent epidemiologic studies and clinical trials have indicated that long-term use of NSAIDs can decrease the incidence of several cancers. Aspirin and other NSAIDs were shown to have effective chemopreventive action against colorectal adenomas, precursors of colorectal cancer. Studies evaluating the association between colorectal adenomas and genetic variability in enzymes, receptors, and signaling molecules in the PG/EGFR pathway are ongoing. A case-control study showed that the risk of melanoma was decreased 40% for subjects who took NSAIDs compared with those who did not. Investigation on whether regular use of NSAIDs has a chemopreventive effect on melanoma risk is presently ongoing at EGRP. A population-based, case-controlled study yielded one of the most provocative new findings. The results of this study showed a 40% lower risk of Hodgkin lymphoma among individuals who took at least two aspirin tablets per week in the preceding five years, compared with individuals who consumed less than two tablets per week.

The use of NSAIDs for chemoprevention is not ideal because of unacceptable side effects, which makes it crucial to develop more effective chemoprevention agents





with minimal toxicity. Recent efforts to identify the molecular mechanisms by which PGE<sub>2</sub> promotes tumor growth and metastasis may provide opportunities for the development of safer strategies for cancer prevention and treatment. Researchers aim to assess how inflammation leads to cancer, which will advance development of new drugs to reduce inflammatory response and aid in tailoring chemoprevention to maximize benefits and minimize drug toxicity.

Despite extensive multidisciplinary research, the inflammatory response and the complex mechanisms leading to cancer remain a major scientific challenge in all areas. Studies are ongoing to evaluate the association between cancer, risk, and candidate genes and cancer, such as enzymes and receptors linked to the synthesis of PGs and related arachidonate metabolites.

### **PROGRESSION, RECURRENCE, MORTALITY, AND DEVELOPMENT OF NEW PRIMARY CANCERS**

DCCPS has a major focus on outcomes after a diagnosis of cancer, and many parts of the organization work together to understand these outcomes. The Office of Cancer Survivorship conducts and supports research that both examines and addresses the long-term and short-term

physical, psychologic, social, and economic effects of cancer and its treatment among children and adult survivors of cancer and their families. The DCCPS Applied Research Program studies demographic, social, economic, and health system factors as they relate to providing preventive, screening, diagnostic, and treatment services for cancer and also coordinates and sponsors research to measure, evaluate, and improve the outcomes of cancer care. The Clinical and Translational Epidemiology Branch in EGRP is the locus for providing support for research that focuses on environmental and genetic factors that influence development of cancer among persons with underlying diseases and conditions, the progression and recurrence of cancer and related mortality, and the development of new primary cancers.

#### **GENETIC AND ENVIRONMENTAL FACTORS HAVE AN EFFECT ON PROGRESSION AND RECURRENCE**

##### **Challenge**

It was evident that cancer-directed therapies do not halt the progression of cancer in many people and that in many other people with cancer, recurrence or another cancer seemingly independent of the first developed. As increasing numbers of persons began to survive an



initial cancer, these long-term outcomes became increasingly important. For example, DCEG, together with the Surveillance Research Program in DCCPS, published a monograph describing the patterns of occurrence of new malignant diseases among U.S. cancer survivors. Key findings were that new cancers were common and certain patterns had been observed that were consistent with the major approaches used in cancer epidemiology—cohort and case-control studies—including a role for tobacco and alcohol, nutrition and hormones, immunosuppression and infections, and treatment effects. The results of studies indicated differences among population subgroups with respect to the risk for recurrence, survival, and new primary cancers even when major known factors, such as type of treatment, were taken into account. Especially until the 1990s, funded cancer epidemiology research had tended to focus on gene and environmental interactions in etiology, risk, and prevention, rather than on the identification of predictors of prognosis.

### Response

Cancer survival is determined by more than the stage at which the cancer is diagnosed. The advances made in understanding the causes of cancer enabled researchers to investigate the factors determining cancer survival or prognosis, and several different factors were found to contribute to long-term outcome. The success of chemotherapy may be affected by variants in genes that metabolize chemotherapeutic agents. Genes that control DNA repair, protection from oxidative damage, and DNA methylation were also found to have an impact on

survival. EGRP has supported research in all these areas, with the goal of identifying genetic polymorphisms that are either protective or deleterious and the environmental factors with which they interact.

DCCPS supported a wide range of studies on some of the many genetic and environmental factors that may be involved in survival, recurrence, and new primary cancers. One technical approach has been especially successful for studying the influence of prediagnosis lifestyle factors on post-cancer outcomes. This approach involves using data obtained from studies of cancer etiology to also study these cancer outcomes. These cohort and case-control studies provide a better understanding of the role of these and other factors in the development of new cancers as well as recurrence, progression, and survival. The development of well-designed biospecimen repositories, now commonplace in epidemiology studies supported by NCI, has further enabled research on genetic factors and cancer outcomes.

### Progress

Since 1997, investigators have made substantial progress on many fronts. Among the lines of research on recurrence, survival, and new primary cancers that have flourished over this time are those involving lifestyle and behavior factors prior and/or subsequent to a cancer diagnosis, genetic factors, and interactions of these effects with cancer-directed therapy.

Pharmacogenomics is an area of study

concerned with interindividual differences in the metabolism and effect of medications due to genetic differences. Certain variants involved in the metabolism of chemotherapeutic agents, DNA repair, cell cycle, and other pathways may be involved in both the survival from a cancer and the risk of new primary cancers. For example, research results on several different kinds of cancer in adults and children suggested that polymorphisms in genes that metabolize methotrexate, cyclophosphamide, platinum-based agents, and tamoxifen are important for the prognosis and progression of an individual's cancer. Polymorphisms in the MTHFR gene, which is involved in processing folate, appeared to contribute significantly to the rate of cancer recurrence. Chemotherapy and radiotherapy may also affect DNA methylation of genes, possibly increasing the risk of second cancers in those treated for cancer with these modalities. The results of these studies and possibly future genome-wide association studies of cancer outcomes may help to better tailor treatments for patients with cancer.

In addition to the extensive research in the area of proteomics, many investigators have returned to the use of immunohistochemistry in a semiquantitative manner to assess the effect of the expression of different proteins on prognosis. The number of proteins now being investigated has grown substantially since 1997. Researchers are developing prog-

nostic models that utilize data on expression of multiple proteins as well as other factors such as ethnicity and genetic polymorphisms. The goal for EGRP researchers in the next decade will be to integrate all of these different sources of data to improve predictive models of cancer risk, relapse, and occurrence of second cancers. This may lead to a great leap forward in delivering personalized cancer treatment.



# SECTION 3: CANCER PREVENTION AND CONTROL

## MEETING THE CHALLENGE

**T**he findings of research over the past decade, including sophisticated statistical modeling, have clearly demonstrated that prevention is the most successful and cost-effective way to address the challenge of reducing the burden of cancer. As many as 50% to 75% of cancer deaths are caused by human behaviors, and evidence-based strategies that lead to lifestyle changes, such as preventing and treating tobacco use, reducing sun exposure, and promoting healthy diet and exercise have substantially decreased the overall incidence of cancer in the United States. Indeed, most of the reduction in cancer-associated morbidity and mortality is a direct result of one specific behavior change: smoking cessation. The contribution of tobacco control to a reduction in the cancer burden was in part enabled by DCCPS funding that helped to identify effective tobacco control interventions at the individual, community, and societal levels and to track the effect of tobacco control among local, state, and national populations.

During the past 10 years, DCCPS has undertaken a major effort to evaluate, strengthen, and expand both the breadth of the prevention research program and the expertise of the scientists who lead it. In addition to such traditionally supported areas of research as smoking, physical activity, and diet, support has been expanded for interdisciplinary sciences in such fields as risk communication, decision-making, sociocultural research, consumer health informatics, policy analysis, neuroscience, and behavioral genetics.

DCCPS and its funded researchers have generated a substantial amount of data on risk-reducing preventive strategies to decrease the incidence of cancer as well as its associated morbidity and mortality. DCCPS will continue to provide grants for research, particularly in the behavioral sciences, to identify improved methods for changing personal lifestyles and to promote informed decisions about health-related behaviors. The ultimate goal is to ensure that the lessons learned from research data are better used to reduce

## THE EXPECTATION — *From the Cancer Control Review Group Report, 1997*

*NCI must make a long-term commitment to develop a more balanced partnership between the biomedical and behavioral/public health paradigms to continue to reverse the upward trend in cancer mortality.*

*The reliability and effectiveness of electronic communication and informatics must be tested through rigorous research if they are to make a meaningful impact on reducing the cancer burden.*

*Increase the focus on interventions with children and youth in order to establish preventive behaviors for the next generation.*



cancer rates more rapidly by informing clinical and community practice and fostering the implementation of evidence-based approaches.

## SCIENTIFIC ACCOMPLISHMENTS FROM NCI'S INVESTMENT TOBACCO CONTROL

**T**obacco use remains the nation's leading cause of preventable premature death, responsible for an estimated 440,000 deaths in the United States each year. Cigarette smoking alone causes approximately 30% of cancer deaths annually, including 87% of lung cancer cases. Thus, lung cancer associated with tobacco use is one of the easiest cancers to prevent; however, it is one of the most difficult cancers to treat effectively. Cigarette smoking is also an important cause of heart disease, stroke, and chronic lung disease, and smoking during pregnancy can cause stillbirth, low birth weight, sudden infant death syndrome, and other serious pregnancy complications. Additionally, exposure to secondhand smoke is a major public health concern; many Americans who do not smoke themselves are exposed to secondhand smoke in public places, workplaces, and homes.

The publication of the landmark first Surgeon General's report on smoking and health in 1964 was a pivotal event in the history of public health. Since that time, there has been a broad societal shift toward less acceptance of tobacco use, accompanied by dramatically increased public awareness of its extraordinary health hazards. Today, more than half of all living Americans who have ever smoked have quit, and the overall prevalence of smoking among adults decreased from 40.4% in 1965 to 20.9% in 2005. It has been estimated that between 1991 and 2003 alone, tobacco control efforts have prevented at least 146,000 lung cancer deaths in men. However, 45.1 million Americans, or one in five, still smoke, and rates are higher in certain populations, such as low-income populations, people with lower levels of education, and some racial/ethnic groups. Additionally, smoking by youths and young adults remains a persistent problem; today, 23.0% of high school seniors are current smokers, as are 24.4% of young adults 18–24 years old. Improving efforts to prevent young people from starting to smoke and helping all those who use tobacco products to quit, remains a critical challenge for the nation.



There is now a strong science base supporting the effectiveness of clinical and community-based tobacco control interventions, media campaigns, and tobacco control policies. Many states and cities have implemented comprehensive clean indoor air laws, which protect nonsmokers from secondhand smoke and facilitate smokers' efforts to quit, or have increased tobacco taxes, an effective means to decrease tobacco use by adults as well as youth, the most price-sensitive smokers. Additionally, the National Network of Quit-lines, which NCI helps support, has greatly increased access to information and support for quitting. However, research is needed in a number of areas, including studies to develop more and better behavioral and pharmacotherapeutic approaches to smoking cessation; to determine how to improve prevention and control of tobacco use among populations at high risk, such as low-income smokers and people with mental health and substance abuse disorders; to increase consumer demand for effective treatment; to better understand the role of the tobacco industry in promoting tobacco use; to gain knowledge on the characteristics and health effects of different tobacco products; to accelerate implementation of effective policies and programs; and to explore ways to change health care systems to enhance tobacco control.



An essential strategy of DCCPS efforts in tobacco control over the past decade has been the enhancement of collaboration and coordinations with federal and non-governmental organizations. The leveraging of resources and expertise with partners, such as the CDC's Office on Smoking and Health, has enabled NCI to strengthen our scientific discovery role while accelerating the translation of science into clinical and public health practice.

#### "LIGHT" OR "LOW TAR" CIGARETTES: TOBACCO PRODUCT DESIGN AND THE EFFECT ON HEALTH RISK

##### Challenge

As the dangers of cigarette smoking became known to the public, tobacco companies introduced a range of new

**T**he **Centers to Reduce Cancer Health Disparities (CRCHD)** is the organizational locus at NCI for efforts to support the training of minority investigators and reduce the unequal burden of cancer in our society. The Center directs the implementation of programs that advance understanding of health disparities in community settings. CRCHD's Community Networks collaborate with DCCPS's Tobacco Research Network on Disparities (TReND).

cigarettes with filters and lower levels of tar and nicotine when measured by a standardized machine testing protocol. Manufacturers heavily marketed these cigarettes with promises of reduced exposure and implied promises of reduced risk. However, the machine-measured yields of tar and nicotine of these so-called light or low tar cigarettes did not reflect what the consumer actually inhaled. This discrepancy resulted from design features of the cigarettes, such as ventilation holes, that allowed smokers to obtain much higher levels of tar and nicotine from the cigarettes than when they were smoked by a machine. Many smokers switched to these cigarettes, mistakenly believing they were less harmful than others. But because the smokers were addicted to nicotine, they changed the way they smoked individual cigarettes to preserve their daily intake of nicotine.

### Response

DCCPS funded research to better understand the health risks, marketing, and public understanding of risks and reasons for smoking “light” cigarettes and published a monograph describing the findings.

### Progress

Studies showed that machine-measured tar and nicotine yields do not provide meaningful information on the amount of tar and nicotine that smokers will receive from a cigarette and are not a meaningful way for smokers to compare the amount

of tar and nicotine that they will receive from smoking different brands of cigarettes. In addition, research indicated that many smokers use terms such as “light,” “ultra-light,” and others as a guide to selecting brands of cigarettes because they believe that such cigarettes are less likely to cause health problems. Thus, advertising and marketing of “light” cigarettes may have promoted smoking initiation and decreased smoking cessation.

The experience with “light” cigarettes has resulted in a greater appreciation of the importance of studying and monitoring the changing cigarette product. Some health education efforts have now targeted consumers’ misperceptions of the health risks of “light” cigarettes; for example, NCI produced a fact sheet and the Centers for Disease Control and Prevention developed a television advertisement. In her August 2006 ruling in the Department of Justice lawsuit against the tobacco industry, U.S. District Judge Gladys Kessler required that tobacco companies eliminate the use of misleading descriptors in brand names and packaging, citing the findings of NCI-supported studies, among others; the case is on appeal at the time of this writing. In addition, the World Health Organization’s Framework Convention on Tobacco Control encourages ratifying nations to prohibit the use of terms such as “low tar,” “light,” “ultra-light,” or “mild” on cigarette products; Brazil and the European Union have already instituted such bans.



A comprehensive analysis of behavioral, toxicologic, and epidemiologic evidence confirmed that while the design of cigarettes has changed over the last 50 years, the health risks have not. The only known way to reduce the enormous health risks of smoking cigarettes is to quit completely.

### SMOKING IN THE MOVIES INCREASES SMOKING AMONG ADOLESCENTS AND YOUNG ADULTS

#### Challenge

Each day in the U.S., more than 4,000 adolescents tried cigarettes and another 1,140 became daily cigarette smokers. Nearly one in four (23%) of 12th graders had smoked in the past 30 days. Reducing the rate of smoking among youths represented a critical public health challenge, because a large majority of adult smokers had begun smoking before they were 18 years old. A number of factors were already known to be associated with youth smoking, including low socioeconomic status; low academic achievement; smoking by peers, siblings, and parents; and exposure to tobacco advertising. However, researchers expressed concern that depictions of smoking in movies and other entertainment media may also have a negative impact on children, adolescents, and young adults.

#### Response

DCCPS funded a number of studies designed to evaluate the influence of smoking in the movies on smoking by

adolescents and young adults. These include a content analysis of major box office hits every year to identify smoking depictions, an assessment of the influence of movie smoking on adolescents, and an assessment of parenting practices and adolescent movie watching. The quantitative data provided insight on smoking prevalence in movies and an opportunity to investigate the mechanisms underlying the effect of exposure to smoking in movies on smoking behavior in adolescents and young adults.

#### Progress

DCCPS-funded work demonstrated that smoking in the movies is a major contributor to youth smoking. These studies demonstrated a dose-response relationship between exposure to smoking in the movies and adolescent smoking initiation, with adolescents who were highly exposed to smoking in movies being nearly three times as likely to start smoking as those who were lightly exposed. Adolescents who had the greatest exposure to smoking in movies were twice as likely to become established smokers compared with those who had the least exposure. This effect was independent of age or the smoking status of a parent, sibling, or friend. Research also found that smoking in movies had an impact on young adults 18–25 years old; the more a young adult was exposed to smoking in the movies, the more likely he or she was to have smoked in the past 30 days or to have become an established smoker.







Because U.S. movies are marketed and distributed all over the world, this research could have far-reaching public health implications. Several major health organizations support proposed initiatives to decrease youth's exposure to movie smoking. These initiatives include assigning an R rating to new movies in which smoking is depicted, requiring strong antismoking advertisements to run before or after the movie, eliminating the identification of tobacco brands in movies, and

increasing parental monitoring of children's movie-watching. Additionally, beginning in 2003, State Attorneys General have written to members of the film industry to encourage them to reduce smoking in movies. In May 2007, 31 Attorneys General wrote, in part, "[E]ach time a member of the industry releases another movie that depicts smoking, it does so with the full knowledge of the harm it will bring to children who watch it..."

**C**OLLABORATIVE INITIATIVES TO REDUCE TOBACCO USE DCCPS works collaboratively with national and international partners to control tobacco use among all segments of the population. The **National Tobacco Cessation Collaborative (NTCC)** was formed in June 2005 to improve the public's health by increasing successful cessation among tobacco users in the U.S. and Canada. The **Youth Tobacco Cessation Collaborative (YTCC)** was formed in 1998 to help accelerate progress in helping young people to quit smoking. YTCC members work collaboratively to co-fund research projects, share plans, and increase attention to the issue of youth cessation. In 2004, DCCPS partnered with the American Legacy Foundation to implement the **Tobacco Research Network on Disparities (TReND)** whose mission is to understand and address tobacco-related health disparities. TReND is designed to stimulate new studies, challenge existing paradigms, and address significant gaps in research on understudied and underserved populations. DCCPS and the other collaborative members of NTCC, YTCC, and TReND represent major organizations that fund research, program, and policy initiatives related to tobacco prevention and cessation, as well as other committed organizations with a vested interest in eliminating tobacco use.





## ENHANCED UNDERSTANDING OF TOBACCO USE AND NICOTINE ADDICTION PROVIDES INSIGHT FOR DEVELOPMENT OF NEW SMOKING CESSATION INTERVENTIONS FOR ADULTS

### Challenge

One-half of all long-term smokers, especially those who began smoking as adolescents, will die prematurely from tobacco use. However, smoking cessation allows people to avoid much or all of the negative health effects of tobacco use, especially when cessation occurs early in life. Of the approximately 44.5 million adult smokers in the U.S., an estimated 70% had noted a desire to quit smoking; indeed, about 40% had made a serious quit attempt. However, fewer than 5% had succeeded in any given year. Encouraging and assisting

more smokers to successfully quit smoking remained a critical national challenge.

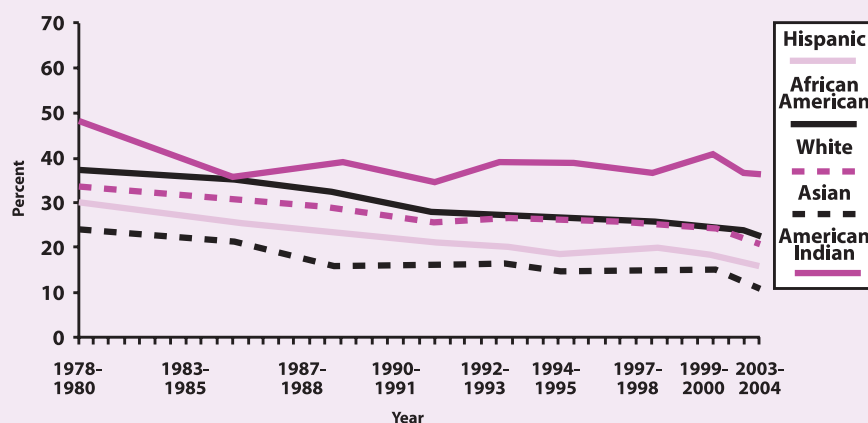
### Response

NCI funded numerous behavioral and pharmacologic studies to better understand nicotine addiction and to identify effective interventions for smoking cessation.

### Progress

NCI research contributed to the development of numerous effective smoking interventions, including nicotine replacement therapies (e.g., gum, patch, lozenge, spray, inhaler), two non-nicotine smoking cessation medications (i.e., bupropion, varenicline), brief and extended counseling, proactive telephone counseling, and motivational interviewing. Nicotine replacement therapies alleviate craving

### Cigarette Smoking Trends among Adults, by Race/Ethnicity, 1978-2004



Source: National Health Interview Surveys, 1978-2004, selected years, aggregate data

Before 1992, current smokers were defined as persons who reported having smoked  $\geq 100$  cigarettes and who currently smoked. Since 1992, current smokers were defined as persons who reported having smoked  $\geq 100$  cigarettes during their lifetime and who reported now smoking every day or some days.

and withdrawal by providing medicinal nicotine to tobacco users in a nonaddictive, safer formulation. Although the precise mechanism by which bupropion enhances the ability of patients to abstain from smoking is unknown, it is presumed that it blocks pathways in the brain relating to the craving of smoking. Varenicline, the newest medication for smoking cessation, has the dual effect of blocking the reinforcing properties of smoking while simultaneously alleviating craving and withdrawal.

The field of pharmacogenetics is generating new knowledge about genetic factors that influence the efficacy of different smoking cessation interventions for different people. The interaction of genetic factors with environmental factors is a fruitful area of inquiry. Environmental factors such as culture, socioeconomic status, family discord, stress, and peer smoking interact with genetic factors to determine susceptibility to, development, and progression of nicotine dependence and smoking behaviors. Maternal smoking during pregnancy, for example, has been found to be a risk factor for subsequent nicotine dependence among offspring. Genetic research on the etiology of nicotine dependence provides new avenues for identifying novel and more effective behavioral and pharmacologic treatment approaches. Recent work, for example, illustrates emerging research in pharmacogenetics exploring how genetic variation in drug-metabolizing enzymes and drug targets

can influence responses to pharmacotherapies. A genetic variant (variant form of the CYP2B6 gene) present in nearly half of Americans of European ancestry is linked to greater effectiveness of the smoking cessation medication bupropion. People with this variant were less likely than those without it to have resumed smoking six months after treatment with bupropion.

#### HMOs INVESTIGATING TOBACCO (HIT): EVALUATING TOBACCO CESSATION SERVICES AS PRIMARY PREVENTION OF CANCER

##### Challenge

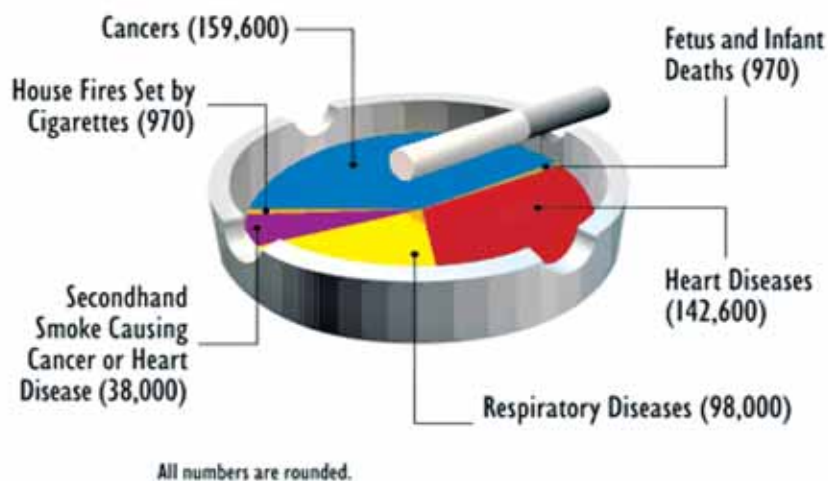
A clear set of evidence-based practice guidelines developed for primary care providers had been strongly endorsed by health care organizations, many of which had conducted dissemination programs. However, the implementation of proven tobacco cessation interventions designed specifically for primary care settings had been disappointingly slow. Because clinician recommendation had been shown to lead to increased rates of smoking cessation, it was essential for primary care clinicians to enhance their efforts to discuss cessation interventions with their patients.

##### Response

Two HIT studies were conducted within the Cancer Research Network, a large consortium of research organizations affiliated with nonprofit HMOs. The first HIT study involved a detailed review of

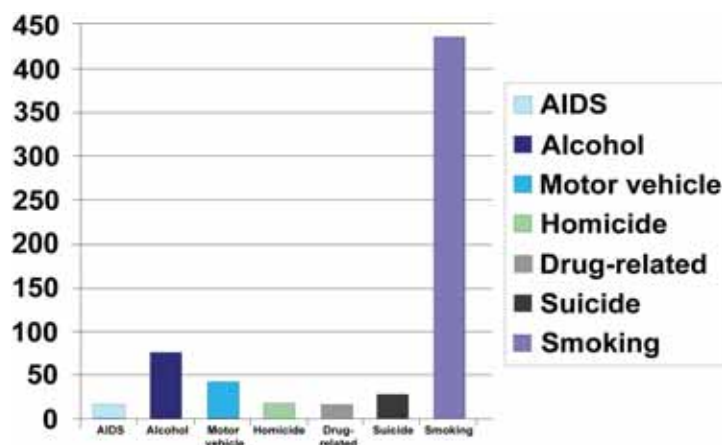


## Deaths caused by smoking each year



Source: 2004 Surgeon General's Report: The Health Consequences of Smoking. CDC 2004.

## Comparative Causes of Annual Deaths in the United States



Sources: (AIDS) *HIV/AIDS Surveillance Report, 2004*; (Alcohol) CDC. (2004). *MMWR*, 53(37), 866-870; (Motor vehicle) National Highway Transportation Safety Administration. (2005); (Homicide) NCHS. *Vital statistics, 2002*; (Drug-related) Mokdad, A.H., Marks, J. et al. (2004). Actual causes of death in the U.S., 2000. *JAMA*, 29(10), 1242; (Suicide) NIMH. (2003 [updated 2006]). *In harm's way—Suicide in America*; (Smoking) SAMMEC, 1995.

tobacco control policies in nine medium and large HMOs and a subsequent survey of more than 4,000 randomly selected smokers who had been seen in primary care in the previous year. Additional surveys were conducted with primary care physicians in the HMOs.

The second HIT study addressed the delivery of tobacco cessation services to primary care patients as recorded in the electronic medical record. Because much of the information of interest was recorded in free-text notes, the project developed a natural language program to code these notes to provide a valid measure of delivery of the recommended services.

### Progress

According to three annual surveys of the HMO health plan managers, all of the health plans had written guidelines for tobacco control that became more comprehensive over the span of the study. However, surveys of smokers showed that many were not receiving assistance in quitting. Greater attention to providing evidence-based smoking cessation services to all smokers will substantially reduce the rate of tobacco use.

Using electronic medical records to monitor and guide the process of delivering tobacco cessation services in primary care was found to be practical, as the natural language processing program provided a valid measure of tobacco control services in four HMOs. In the final phase of the HIT study, currently underway, the information from electronic medical records is being used in an individually tailored physician feedback intervention designed to improve the performance of primary

care physicians in the delivery of tobacco cessation services.

## DIET, WEIGHT, AND PHYSICAL ACTIVITY

Diet, weight, and physical activity play important roles in the prevention of cancer. A diet rich in fruits and vegetables lowers the risk of several cancer types, yet studies have shown that the U.S. population consumes far less than the recommended 4 to 13 servings of fruits and vegetables daily. In addition, the rate of overweight and obesity has increased substantially over the past decade (Figure, page 48), raising the risk of several major cancers, including colon, breast, endometrial, renal, and esophageal cancers. In fact, it is estimated that obesity and physical inactivity cause 25% to 30% of these cancers. For colorectal cancer alone, physical activity has been found to reduce the risk by 50%.

The behavioral research program has been enhanced to support interdisciplinary sciences to better understand health habits and to develop education and tools to help individuals lower their risk for cancer through better diet and increased physical activity. Educational programs must be directed at youth as well as adults, as healthy habits integrated early in life offer the most benefit and have the highest potential for long-term success.

Researchers are now focusing on energy balance, or the integrated effects of diet, physical activity, and genetics on growth and body weight over an individual's lifetime, and on how those factors may influence cancer risk. In 2005, the Transdisciplinary Centers on Energetics and Cancer (TREC) initiative was







launched. This five-year scientific research effort is aimed at reducing the incidence of cancer associated with obesity, poor diet, and low levels of physical activity. Also, NCI researchers have developed biostatistical models and objective methods to help obtain accurate measures of dietary and physical activity behaviors. (See Section 6, “*Monitoring, Reporting, and Disseminating Progress*.”) These efforts are integral to enhancing the capacity to monitor trends in diet, weight, and physical activity.

#### **BODY & SOUL: A WELLNESS PROGRAM FOR BLACK CHURCHES**

##### **Challenge**

The black population is at high risk for obesity, as well as many other serious and often fatal diseases, including cancer. More programs promoting better diet were needed for this population.

##### **Response**

NCI established partnerships with a wide variety of federal, nonprofit, and private organizations to help support a nation-



wide program to reduce the risk of diseases associated with poor diet by promoting better dietary habits (e.g., eating more fruits and vegetables) among the black population. The program, *Body & Soul* ([www.bodyandsoul.nih.gov](http://www.bodyandsoul.nih.gov)), was based on the findings of two efficacy studies funded by NCI as part of the 5-A-Day initiative and was designed to draw on the influence of the church in the black community. The church-based program supported healthy eating through pastoral leadership, educational activities, and peer counseling.

##### **Progress**

The *Body & Soul* program had significant effects on mediators (e.g., social support, self-efficacy) that were predictive of subsequent dietary change for fruit and vegetable intake. In churches that have implemented the program, healthy options are available at events where food is served and members have responded positively to health-related activities and peer counseling. The program has expanded into a self-sustaining, nationwide community partners' network and has been integrated into black churches around the country. The program is an exemplary model of translating research into practice.

## PHYSICAL ACTIVITY AND DIET INTERVENTION WITHIN PRIMARY CARE AND HOME SETTINGS IMPROVES HEALTH BEHAVIORS AMONG YOUTHS

### Challenge

Between 1997 and 2007, there was a dramatic rise in childhood and adolescent obesity, which increased the risk of adult obesity and, consequently, chronic disease.

### Response

DCCPS funded the Patient-Centered Assessment and Counseling for Exercise Plus Nutrition (PACE+) project for adolescents. This intervention, based on the successful Physician-Based Assessment and Counseling for Exercise (PACE) project for adults, involved primary care providers, tailored interactive computer programs, and telephone counseling to improve the key health behaviors of children 11 to 15 years old.

### Progress

Research showed that several factors were associated with physical inactivity and dietary intake in adolescents. The factors contributing to physical inactivity differed according to sex, with family support, television/video rules, and characteristics of the neighborhood environment being associated with physical inactivity among girls and being of an ethnic minority, overweight, and confidence about reducing sedentary behaviors being associated with physical inactivity among boys. Family influence, household rules about eating, and strategies for change were key correlates of better dietary intake among both adolescent boys and girls.

Physician counseling combined with interactive programs and counseling was effective for modifying important health

behaviors linked to obesity among adolescents. PACE+ increased physical activity among adolescent boys and improved dietary behavior (e.g., reduced saturated fat intake) among adolescent girls during a one-year period. Adolescents reported high satisfaction with all aspects of the intervention. Dissemination of obesity prevention programs initially through pediatric and/or primary care settings may prove useful in preventing adolescent obesity. In addition, identification of the family, neighborhood, and psychological factors that influence childhood obesity may assist in the development of future interventions or programs to further prevent or reduce obesity among adolescents. Developing interventions for multiple health behaviors, rather than a single health behavior, represents an efficient and useful strategy for modifying important health behaviors.

## UNDERSTANDING CANCER RISK

A better understanding of the probability that cancer will develop in an individual over a defined period of time can help efforts to create cancer prevention strategies. The number of cancer risk models in



the U.S. has grown steadily since the late 1980s, when researchers first published models that predicted a woman's risk of breast cancer on the basis of known risk factors. Since then, statistical models have become widely used by physicians to identify individuals at high risk of cancer who may benefit from targeted screening or other interventions, and to make decisions about cancer treatment.

Cancer risk prediction models have several other important applications, including the planning of intervention trials, the creation of benefit-risk indices, the estimation of the cost of the population burden of disease, the design of population prevention strategies, and the improvement of clinical decision-making (genetic counseling). Investigators are evaluating cancer risk models to identify their strengths and limitations and to explore methodologic issues related to their development, evaluation, and validation. Research priorities include revising existing breast cancer risk assessment models and developing new models, encouraging the development of new risk models for other types of cancer, obtaining data to develop more accurate risk models, supporting validation mechanisms and resources, and promoting effective cancer risk communication and decision-making.

## MODELS REFINE CANCER PREDICTION

### Challenge

As the number and sophistication of cancer risk prediction models grew, it became increasingly important to ensure that the models were correctly developed and rigorously evaluated. An important aspect in the development of risk models is to obtain accurate relative risk and attributable risk estimates for etiologic factors, such as demographics, reproductive history, smoking habits, dietary patterns, medications, genetic factors, and clinical and biologic markers, and to determine how these factors act jointly on risk. The most important characteristics of risk model performance are calibration, discrimination, and accuracy.

### Response

Cancer researchers, clinicians, and the general public began to devote more attention to statistical models designed to predict the occurrence of cancer, an individual's response to treatment, and the effectiveness of chemoprevention drugs. DCCPS investigators led a number of initiatives moving the field of cancer prediction from its infancy into a growing and promising scientific field of high-quality prediction models.

**T**he **Division of Cancer Prevention (DCP)** is the primary unit of NCI devoted to cancer prevention research. DCP projects address the need to identify where a person is in the process of carcinogenesis, and to determine ways to actively intervene to stop it from becoming invasive cancer. Varied approaches are supported, from pre-clinical discovery and development of biomarkers and chemoprevention agents, including pharmaceuticals and micronutrients, to Phase III clinical testing. Programs are harmonized with various NIH institutes, and federal and state agencies, and other NCI divisions such as DCCPS. It is the role of DCCPS to subsequently monitor and evaluate the application of and outcomes related to early detection and evidence-based cancer prevention methods.



### Progress

NCI investigators made advances in an established risk model as well as in new models. The Gail Breast Cancer Risk Assessment Model was validated in four different population studies and was also used to design two chemoprevention trials for breast cancer. Among the new models were more than five different breast cancer susceptibility models. These models were developed to help geneticists, genetic counselors, and their patients decide whether genetic testing should be done to determine the presence of the BRCA1 or BRCA2 susceptibility genes. In addition, NCI researchers are leading the development of the first risk prediction model to estimate the probability of colorectal cancer within a specified interval in individuals 50 years and older. Estimates of the probability of colorectal cancer will be useful for counseling patients about screening, for planning chemoprevention and screening intervention studies, and for estimating the population burden and potential impact of interventions.

#### EFFICACY OF AND PSYCHOSOCIAL OUTCOMES AFTER PROPHYLACTIC MASTECTOMY

### Challenge

Prophylactic mastectomy (bilateral or contralateral) was introduced in the mid-1990s as a method of preventing incident or recurrent breast cancer. Several aspects of this procedure were unknown, most notably, how commonly the procedure was performed in the community, how efficacious it was, and what impact it had on a woman's quality of life.

### Response

Scientists participating in the Cancer Research Network designed a series of studies to address the efficacy of prophylactic mastectomy and its associated long-term quality-of-life outcomes. Initially, the scientists focused on the extent to which prophylactic mastectomy prevented subsequent breast cancer events and breast cancer-related death. Subsequent studies focused on the quality-of-life and psychosocial outcomes after prophylactic mastectomy.

### Progress

Bilateral or contralateral prophylactic mastectomy was found to be performed infrequently, with the latter procedure being done slightly more often. With either procedure, the risk of breast cancer was reduced by more than 95%, and approximately 85% of women were satisfied with their decision to have the procedure. Contentment with quality of life did not differ between women who did and did not have a prophylactic mastectomy and was instead driven by general health perception, possible depression, and other psychosocial factors.

Among women who had a contralateral prophylactic mastectomy, satisfaction with their decision was associated with being an active participant in the decision, which was in turn more common among younger, college-educated women. The results of this research reassured women and their clinicians in community practice considering this procedure. In addition, the results called attention to the need for ensuring that women were well-informed and for encouraging them to participate in decision-making with their clinicians.



# SECTION 4: DETECTION AND DIAGNOSIS

## MEETING THE CHALLENGE

**A**lthough screening clearly had a role in breast, cervical, and colorectal cancer care, significant questions remained about whether it was being applied well and was reaching all who would benefit. Until the mid-1990s, cancer-related mortality rates remained relatively stable—even for cervical and breast cancers, two types of cancer for which evidence suggested that screening would save lives. In 1997, screening rates within the appropriate time interval were relatively high for breast cancer and cervical cancer in the general population but were lower among low-income and uninsured populations. At the time, it was known that the Papanicolaou (Pap) test reduced the incidence of cervical cancer and related mortality. Breast cancer screening with mammography was recognized to be efficacious for women 50

years old or more, but ambiguity emerged about the role of screening mammography for women 40 to 49 years old. Evidence confirmed mortality reductions were possible through colorectal cancer screening, but screening rates were low (25% to 30%), despite available guidelines. A lack of evidence from randomized trials led to controversy about the role of prostate cancer screening. The contribution of screening to decreases in mortality related to breast, cervical, colon, and prostate cancers remained ambiguous as the millennium drew to a close, but there were high expectations that more could be done to evaluate and increase the impact of screening.

## THE EXPECTATION — *From the Cancer Control Review Group Report, 1997*

*A high priority for cancer control research with promising returns on investment is screening.*

*Methods are needed for identifying barriers to the use of effective screening modalities, reaching underserved populations, ensuring adherence to recommended screening regimens, including maintenance of repeat screening and promoting physician-patient communication and informed patient decision-making.*

*The emergence of new genetic, diagnostic, and treatment technologies creates new challenges and opportunities for research related to informed consent and decision-making.*



## SCIENTIFIC ACCOMPLISHMENTS FROM NCI'S INVESTMENT

### SCREENING AS A PROCESS

NCI's response to the challenges surrounding cancer screening included forming DCCPS and its programs that would sponsor research to advance the understanding of cancer care and screening implementation. The Applied Research Program (ARP) was developed to help gain an understanding of the economic and health impact of cancer control activities across the cancer control continuum, and the Behavioral Research Program (BRP) was established to stimulate research in communication and behavior relevant to cancer screening and diagnosis. The Surveillance Program (SRP) initiated efforts to monitor cancer trends and better estimate the relative contribution of screening and treatment to mortality reductions.

As DCCPS passes its decade mark, new screening technologies for colorectal, cervical, and breast cancers continue to emerge, but they are on the frontier of practice, and their impact has yet to be determined. Controversy persists about the role of prostate-specific antigen in prostate cancer screening, and no results from randomized trials have been

published to date. Therefore, our knowledge of the impact of screening at the population level relies on technologies that have been in use the longest: mammography and the Pap test. The major advances over the past decade of screening application reflect progress in breast, cervical, and colorectal cancer screening.

### RECOGNITION OF SCREENING AS A PROCESS

#### Challenge

In 1997, the emphasis in screening was on encouraging individuals to use tests and treatments of known efficacy, but it was not clear why mortality rates were generally so tenaciously stable despite increases in screening.

#### Response

DCCPS funded ROIs and cooperative agreements to examine the use of screening in practice and to understand its impact. The research portfolio supported by DCCPS during the past decade included many studies in community and primary care settings. BRP sponsored community studies in populations that were historically underscreened. ARP extended funding of the Breast Cancer Surveillance Consortium and established financial support for the Cancer Research Network.



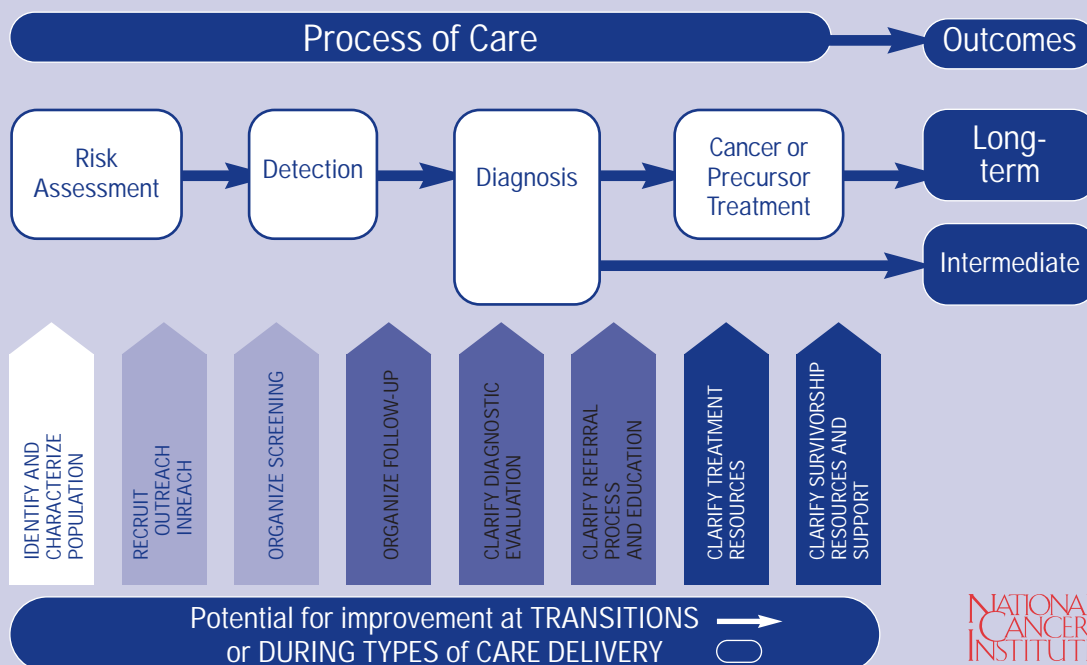
## Progress

In 1997, the view was that an understanding was needed about how to promote screening and measure its impact. The DCCPS response resulted in an evolution of thinking from simple promotion of a test to understanding screening as a process whose success depended on several factors: identifying the individuals at risk for specific types of cancer, offering the screening test to those individuals (known as recruitment), performing the screening test well (detection), ensuring follow-up when the findings of the test are abnormal, and treating the individuals who are diagnosed with premalignant conditions or cancer (see figure below). This is often referred to as a systems approach to screening. Work throughout the first decade of DCCPS helped to identify the relative importance of each of these steps and the need to address

them. When the screening process is done well, few late-stage cancers develop and mortality rates decline. The successful implementation of the entire process is important when considering the impact of cancer screening, as its efficacy is tested in controlled studies in which investigators optimize the steps; in practice, this level of organization across the screening process does not automatically exist. Because not all individuals have or use health care, the systems approach to the problem of screening also includes consideration of how to reach specific communities and increase the likelihood of screening for individuals who may not usually seek care.

A study of the three years preceding the diagnosis of late-stage breast cancer within a managed care system showed that more than 50% of such cancers occurred among women who had not

# SCREENING IS A PROCESS





been screened within an efficacious interval, whereas more than 30% of them occurred among women who had negative screening tests. The smallest proportion of late-stage breast cancers was associated with potential failures during the follow-up process. Similar findings exist for cervical cancer, and these results have been confirmed by those of other studies in the general population, where care coordination is expected to be more challenging. These results suggest that offering screening within efficacious intervals is critical to avoiding late-stage cancer and that the test must be performed well to find the cancer when it is present. Screening research supported by DCCPS has therefore evolved to consider not only the individual attitudes of those who may benefit from the test, but also the attitudes of the clinicians who may be offering the test, the quality of the test being delivered in practice, the completeness of follow-up for abnormal findings, and the context in which screening is offered, as this can affect all the steps of the process.

#### COMPUTER TECHNOLOGY TO IMPLEMENT REMINDERS AND TAILOR INTERVENTIONS

##### Challenge

Time constraints and competing demands for other clinical services prevented many physicians from routinely offering screening tests to their patients, and many more

physicians lacked the time to discuss specific screening choices according to an individual patient's history. Furthermore, recommendations varied among national organizations with respect to when to start screening for breast and cervical cancer and how often it should be performed. For colorectal cancer, more than one test was recommended for screening. The question in 1997 was how to increase the likelihood that screening was offered to people.

##### Response

DCCPS supported investigator-initiated research to increase screening uptake through the development of strategies to increase physicians' recommendations for screening. DCCPS also stimulated research within primary care practices with the program announcement, "Colorectal Cancer Screening in Primary Care Practice," and a call for research on tailored communication through the Centers of Excellence in Cancer Communications Research.

##### Progress

The overwhelming evidence indicating that patients who receive a provider recommendation are more likely to complete appropriate cancer screening tests prompted the design of interventions to improve screening by facilitating changes in provider practice. These strategies often were implemented at the orga-



nizational level and included office reminder systems and prompts as well as staffing and procedural changes, such as engaging nurses and counselors to enhance delivery of services before or after the clinical encounter. Tools that reminded patients that they were due or late for screening were also found to increase screening ([www.thecommunityguide.org/cancer/](http://www.thecommunityguide.org/cancer/)). More intensive follow-up strategies, such as phone calls following initial reminder letters, can be cost-effective in reaching rarely screened groups.

The advances in computer technology of the past decade allowed not only the generation of computerized reminder systems, but also a shift away from a one-size-fits-all approach to screening promotion toward a personalized approach called “tailoring.” In tailoring, messages (or strategies) can be created to reach one specific person based on characteristics that are unique to that person. Technologic advances also moved tailored interventions from primarily paper-based to video, CD-ROM, and the Internet, allowing for increased reach, interactivity, and personalization. Interventions can be tailored to fit a patient’s risk profile, demographic information, or other relevant characteristics, such as the individual’s barriers to screening. This approach was used successfully to increase rates of mammography use among different populations of

women, enhance decision-making about BRCA testing, and promote colorectal cancer screening. More recently, tailoring according to cultural variables has been used to address ethnic and cultural differences in screening behavior.

#### INTERVENTIONS TO GUIDE PATIENTS IN DECISION-MAKING FOR SCREENING

##### Challenge

The varying levels of evidence to support screening modalities across cancer types made it difficult for clinicians to offer simple recommendations, even if they remembered to offer screening. The benefit for breast cancer screening was less clear for younger women; three tests existed for colorectal cancer screening (fecal occult blood testing, sigmoidoscopy, colonoscopy), the screening interval for cervical cancer varied from one to three years, and evidence for the benefit of prostate cancer screening was controversial. Making age-appropriate recommendations was challenging and explaining the complexity was an even harder task. The result was that even if providers presented all the options, patients dealing with decisions about cancer screening were often overwhelmed by the number and/or complexity of factors in the decision-making process.



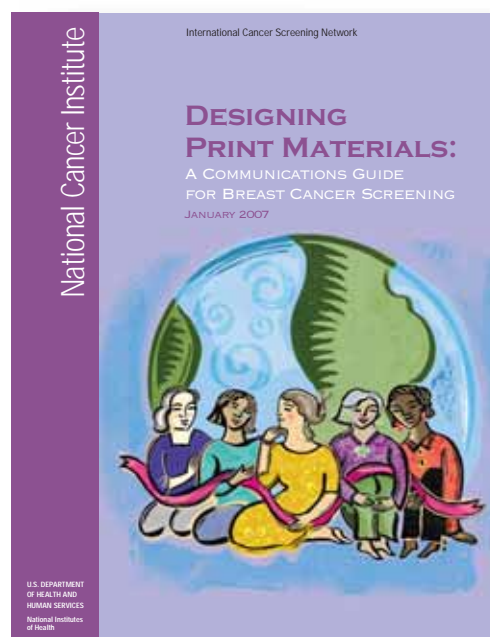


### Response

To encourage research on the cognitive and affective processes underlying decision-making in cancer control, BRP sponsored two program announcements: “Decision-Making in Cancer: Single-Event Decisions” (PA 05-017) and “Decision-Making in Health: Behavior Maintenance” (PA 05-016), and also funded numerous investigator-initiated studies designed to evaluate interventions to help individuals make choices about screening. These interventions were focused primarily on screening for colorectal and prostate cancer and provided information about the different screening tests available, the known outcomes of screening, and the consequences of treatment. In addition, the ARP-sponsored International Cancer Screening Network developed the brochure, *Designing Print Materials: A Communications Guide for Breast Cancer Screening*, a practical guide for improving the quality of information provided by breast cancer screening programs to consumers.

### Progress

Research demonstrated that decision-making interventions increased patients’ knowledge of both screening technologies and the advantages and disadvantages of the choice to have a screening test. Studies of colorectal cancer screening showed that decision-making interventions led to an increased likelihood that an individual talked to his or her health care provider about screening. Overall, the effects of decision-making interventions on screening behavior were small, but the findings suggested that the interventions increased the use of screening tests for which there is strong evidence (such as colorectal and breast cancer screening) and possibly decreased the use of screening tests for which there are no clear evidence-based recommendations (such as prostate cancer screening with prostate-specific antigen testing). The importance of decision-making interventions for cancer screening tests of uncertain benefit is likely to increase as genetic and other new screening tests become available, but the use of decision aids and their implications need further testing.





## INNOVATIVE COMMUNITY-LEVEL METHODS TO REACH POPULATIONS WITH LOWER RATES OF SCREENING

### Challenge

Over the past 10 years, new research had indicated benefits of screening but disparities in screening uptake had emerged. Populations without a health care provider, people who were underinsured or uninsured or who were of some racial/ethnic minorities were much less likely to be screened. The question then was how to reach these communities.

### Response

DCCPS supported outreach interventions in community settings that improved patient adherence to cancer screening recommendations among diverse populations.

### Progress

Although the magnitude of intervention effects tend to be smaller when delivered in communities than in clinical settings, research conducted over the course of 1997–2007 demonstrated that community-based strategies offer particular advantages for reaching populations with low or no screening. The finding of these studies demonstrated that strategies can successfully increase screening among populations labeled as “hard to reach.” Promotion of screening in primary social settings for these populations, such as churches or public housing units, was effective in increasing screening uptake. Interventions were also effective when they addressed the particular sociodemographic, psychologic, and behavioral characteristics of the target population. However, access to screening and follow-up services must also accompany promo-

tional efforts, and interventions reducing or eliminating financial and structural barriers to screening, such as low-cost vouchers or mobile mammography vans, have consistently improved screening rates among populations that typically lack access to services.

Although disparities in screening can be reduced with targeted efforts, evidence-based strategies for improving screening rates in diverse populations have not been routinely adopted into practice. More effort is needed to design interventions that can be easily adapted and sustained beyond research trials. Toward this end, DCCPS encourages ongoing research (through PAR-06-039) to develop, refine, and test models to disseminate and implement research-tested interventions. Research over the past decade also demonstrated that multi-component interventions are needed to address the combination of individual, social, and structural factors that influence screening uptake. The challenge for the next generation of community-based research, however, is to identify which single or minimal combination of intervention components is most effective for improving screening rates among diverse populations and settings.

## SYSTEMATIC METHODS FOR UNDERSTANDING PHYSICIANS' ATTITUDES AND BEHAVIORS

### Challenge

Although health care provider recommendations were known to be a critical aspect of screening, national estimates of provider knowledge and practices were lacking. This was especially challenging for colorectal cancer, for which screening

rates were low and there was a limited understanding about how health care providers influenced initiation of the screening process.

### Response

DCCPS established and funded several national surveys of health care providers and health plans as well as studies of interventions to change provider behavior with respect to better delivery of cancer screening. Colorectal cancer screening was a particular focus of these surveys and intervention studies because of evolving screening guidelines and technologies and low rates of screening. In an effort to evaluate health care provider issues in cancer screening more broadly, DCCPS also developed a national survey of primary care physicians' recommendations and practices for breast, cervical, colorectal, and lung cancer screening and partnered with the Centers for Medicare and Medicaid Services to support its efforts to develop and assess methods for increased colorectal screening uptake among Medicare beneficiaries and their health care providers.

### Progress

A systematic way was developed to sample and survey physicians that provides valid insight into physicians' roles in presenting the option of screening. The findings of these surveys and studies demonstrated that recommendations, policies, and practices for cancer screening and follow-up of abnormal findings vary by physician specialty and practice organization.

Among primary care physicians, there was a high awareness of colorectal cancer screening but gaps in knowledge about the appropriate timing and frequency of screening for average-risk patients, as well as of the need for complete diagnostic evaluation following a positive fecal occult blood test. In addition, many primary care physicians used screening techniques that have been found to be ineffective (e.g., fecal occult blood testing through digital rectal examination).

Among gastroenterologists and general surgeons, surveillance colonoscopy was often performed inappropriately and in excess of guidelines, particularly with respect to hyperplastic polyps and low-risk lesions (such as small adenomas). Information from surveys of health plans showed that, at the time, few had implemented three essential components of colorectal cancer screening delivery: coverage of testing, statement of clear guidelines, and tracking systems to identify the status of individual patients in a clinical practice.

Data collected from surveys of practicing physicians were used to estimate the capacity for delivering screening endoscopy nationally. These data indicated that few physicians involved nurse practitioners and physician assistants in the screening process, despite this being a valid method for increasing screening uptake. In addition, the findings of a pilot study of Medicare populations in North



Carolina and South Carolina showed that more than 25% of individuals had not received a physician recommendation for colorectal screening and that there were racial differences in screening uptake. These data can serve as motivators for the implementation for reminder systems and for the development of methods to present screening options outside of the physician-patient encounter.

The data from these surveys of health care providers have served as an impetus for the development of a variety of initiatives to improve the effective use of colorectal cancer screening. For example, the National Colorectal Cancer Roundtable sponsored the development of the publication, *How to Increase Colorectal Cancer Screening Rates in Practice: A Primary Care Clinician's Evidence-Based Toolbox and Guide* (available at [www.nccrt.org/Documents/General/IncreaseColorectalCancerScreeningRates.pdf](http://www.nccrt.org/Documents/General/IncreaseColorectalCancerScreeningRates.pdf)). The roundtable is also working with professional organizations such as the American College of Obstetrics and Gynecology to educate physicians about the most effective ways of conducting colorectal cancer screening with fecal occult blood testing. In addition, the high number of physicians who reported using ineffective screening with fecal occult blood testing led the American Cancer Society to work with the American Medical Association to revise the CPT code for billing this test so that the code specifies use of the test as a home kit for screening. The survey findings have also stimulated NCI support of further research to better understand reasons for nonadherence to guidelines.

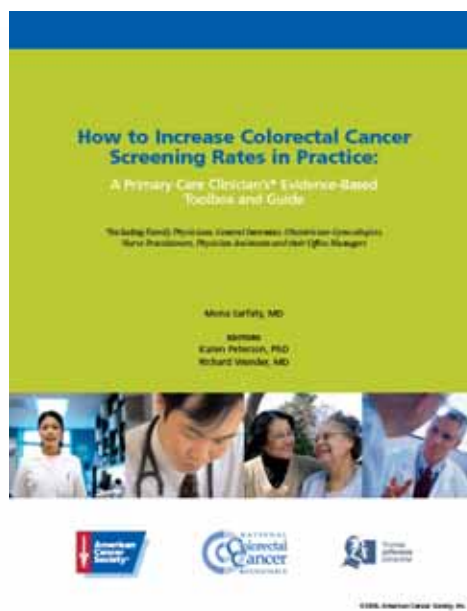
## CERVICAL CANCER SCREENING IN RESOURCE-POOR SETTINGS

### Challenge

The Pap test for cervical abnormalities has been one of the most widely used screening tests in the U.S. since the 1940s. However, it was rarely used in developing countries because resources are not available for the laboratory, technicians, and care necessary to the screening process. As a result, nearly 80% of all cervical cancers occur in developing countries, and the associated mortality is high. In 1997, data about the costs and benefits of alternative screening strategies did not exist.

### Response

DCCPS supported research on cervical cancer control in which the cost-effectiveness of alternative screening methods was evaluated. This research was carried out by a multidisciplinary group with extensive experience in mathematical modeling of human papillomavirus (HPV) and cervical cancer, epidemiologic studies of HPV and cervical neoplasia, cervical cancer screening studies in multiple





countries, and economic evaluation. Data from work sponsored by NCI and results from the cancer registries managed by SRP were used in mathematical models to estimate the impact of screening under a variety of conditions and screening schedules in five developing countries: India, Kenya, Peru, South Africa, and Thailand.

### Progress

Many key findings emerged from this work but one of the most intriguing was the cost-effectiveness of a variety of cervical cancer screening strategies in developing countries. The most cost-effective strategies were those that required the fewest visits, resulting in improved follow-up testing and treatment. In resource-poor settings, screening women once in a lifetime, at the age of 35 years, with a one-visit or two-visit screening strategy involving visual inspection of the cervix, with acetic acid or DNA testing for HPV in cervical cell samples, was a cost-effective alternative to conventional three-visit cytology-based screening programs. The method reduced the lifetime risk of cancer by approximately 25–36% and cost less than \$500 per year of life saved.

This study demonstrated that NCI-funded research had implications for health care



around the world. The underlying model for this study has been applied to problems in cervical cancer control in many other countries, including Canada, the United Kingdom, France, Italy, The Netherlands, Spain, Germany, Hong Kong, China, Tanzania, Columbia, Brazil, and Costa Rica. The study has also provided insights into screening approaches and use of HPV vaccines in the U.S.

### IMPROVEMENTS IN FOLLOW-UP TO SCREENING

#### Challenge

To reduce death from cancer through screening there must be timely and appropriate follow-up for abnormal find-





ings on a screening test. Screening and follow-up can be particularly challenging for low-income and uninsured populations because of the expense and multiple clinic visits involved. Thus, these populations were at particularly high risk for lack of follow-up for an abnormal screening test result. Although routine cancer screening uptake can be initiated by individuals, the identification of an abnormal finding and subsequent follow-up is inextricably tied to a health care provider in a clinical setting within a health care delivery system.

### Response

DCCPS supported studies to identify factors associated with a lack of follow-up to abnormalities detected during screening and to evaluate interventions designed to improve follow-up rates. Because of the major responsibility of health care providers with respect to follow-up to screening, research was directed at the evaluation of provider-related and health care system-related factors.

### Progress

An innovative study of Latina women in underserved communities determined that a single-visit program was successful in increasing the rate of immediate treatment and follow-up of women with high-grade cervical dysplasia according to the Pap test. Other practice-level interventions targeting predominantly minority, medically indigent populations have achieved increases in follow-up rates with the involvement of nurse case managers, tracking systems, reminder calls, scheduling of missed appointments, and clinic staffing with onsite colposcopy.



Another study showed that physician decision-making was the primary reason for a lack of complete diagnostic evaluation as follow-up after a positive fecal occult blood test or positive findings on sigmoidoscopy. Clinics that included academic detailing (one-on-one training), auditing, and a process for notifying patients of a positive fecal occult blood test led to rates of follow-up diagnostic evaluation that were comparable to those for controls.

Systematically incorporating provider-related factors within health care systems has shown promise, especially when physician recommendations are noted in automated tracking systems that report abnormal findings and track completion of procedures that affect follow-up care.

## SCREENING TEST PERFORMANCE

The effectiveness of a screening test depends on its diagnostic accuracy, or how well it identifies disease when it is present (i.e., sensitivity) and how well it produces negative results when disease is absent (i.e., specificity). Initiatives were established to ensure that research was undertaken to identify factors that may affect the diagnostic accuracy of cancer screening tools. Studies were needed not only to determine the diagnostic accu-

racy of cancer screening tools but also to determine other factors that affect the accuracy of such tools, such as physician-related and patient-related factors as well as biologic characteristics.

## ANALYZING THE EFFECTIVENESS AND ACCURACY OF SCREENING

### Challenge

The accuracy of various screening modalities had been evaluated in randomized trials, and quality standards had been established. However, the application of these standards in practice was not known. The quality of Pap test performance had been well established, but the quality of mammography implementation was much less clear.

### Response

Soon after DCCPS was established, it led work on the evaluation of screening in the community setting. For example, the Breast Cancer Surveillance Consortium (BCSC) was established by NCI in 1994 and renewed under ARP on two occasions in the subsequent decade. The BCSC has been a critical leader in understanding how to isolate factors that influence mammography screening performance.

### Progress

BCSC originally consisted of independent centers studying the practice of breast cancer screening in their individual communities, but it was difficult to draw conclusive results from comparisons of similar but heterogeneous data. The ARP led an effort to establish a centralized database of information about women undergoing mammography, increase the

standardization of data collection, and create a central pooled data resource from all of the centers. As a result of this effort, data on more than 5.5 million mammograms from more than 2 million women are now available on a public web site (<http://breastscreening.cancer.gov>). These data provide benchmarks for sensitivity, specificity, and other measures of interpretive performance that did not exist in 1997.

This large, standardized dataset also presents a unique opportunity for investigators throughout the country to study how mammography screening performance may be improved and how breast cancer screening relates to changes in disease stage at diagnosis, survival, and mortality. Researchers from any organization can apply to use BCSC data for their projects, and to date, more than 235 peer-reviewed publications have been published on topics such as disparities in screening, the variation in interpretive performance among radiologists, the effect of screening interval on sensitivity and specificity of mammography, and how screening practices in the United States compare to those in the United Kingdom.



## INFLUENCE OF BREAST DENSITY ON ACCURACY OF MAMMOGRAPHY

### Challenge

In 1997, there were limited data on patient-related factors or biologic characteristics that might influence the accuracy of mammography.

### Response

The longitudinal data and the data collection infrastructure of the BCSC made it possible to explore the role of patient-related factors in the accuracy of detecting breast cancer by mammography.

### Progress

In studies of screening mammography, breast density was associated with higher rates of false-positive results and higher rates of recall for further evaluation. The emergence of breast density as a contributor to mammography accuracy—as well as a risk factor for breast cancer—has led to further research to improve the measurement of breast density, explore factors affecting density, and evaluate interventions to reduce density by discontinuing hormone replacement therapy (identified as a contributor to breast density) before mammography is performed.

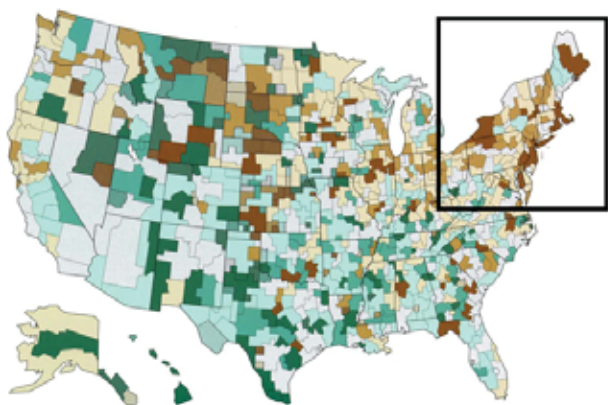
## MEASURING OVERALL IMPACT

Although screening had been shown to be effective in numerous studies, those studies represented controlled environments in which recruitment, use of the test, and follow-up for abnormal findings had been optimized. This level of organization across the spectrum of the screening process does not exist in real-world practice, even in the setting of managed care. Thus, research on screening trends in actual practice is needed in order to fully understand the impact of screening. In addition, investigators determined that factors related to health care systems and health care providers are important contributors to screening uptake. As such, research to evaluate these factors was needed to better understand the influence of health care providers' attitudes and the complexities of health care delivery systems. The success of both old and new screening technologies continue to rely on surveillance of screening process measures, attitudes in the target populations, attitudes of providers, and measurement of cancer outcomes.

## SURVEILLANCE PROVIDES INSIGHT INTO SCREENING TRENDS

### Challenge

In 1997, small studies indicated that cancer screening was more likely among patients who were members of group and staff model HMOs and patients of obstetrician/gynecologists and female physicians, but we did not have a source of comprehensive data about screening that provided representative estimates of





screening rates for the nation and an understanding of factors that influenced those rates.

### Response

In 2000, NCI and CDC collaborated to develop a subset of cancer screening questions on the National Health Interview Survey (NHIS) Cancer Control Supplement (CCS); several questions pertained to colorectal cancer screening, mammography, and prostate-specific antigen testing. NCI and CDC also cofunded a similar CCS to the new California Health Interview Survey (CHIS).

### Progress

The efforts to update these important surveys provided a basis for targeting intervention research and evaluations of factors influencing the use of screening. The subset of questions on cancer enabled researchers to document and evaluate screening rates more thoroughly. Among the key findings was that health insurance coverage was a more proximal predictor of screening than socioeconomic position. Another finding was that the rates of follow-up for abnormal find-

ings on screening mammography differed among black, Hispanic, and non-Hispanic white women, but the differences were explained by sociodemographic characteristics other than race/ethnicity, such as income and age.

The findings led NCI and CDC to refocus screening efforts on improving colorectal cancer screening uptake and on examining the extent to which decisions about cancer screening are informed and shared by individuals and their health care providers. Data from CHIS generated new research on race, ethnicity, acculturation and immigration, and public health. The early finding that cancer screening is less likely in the Asian population, regardless of income, education, or access to care, has been refined by analyses of specific nationalities within the Asian population. Moreover, findings from CHIS at the local level have been used by legislators, public health departments, advocates, and health plans to improve health care and health care policy throughout California.

**T**he Division of Cancer Treatment and Diagnosis (DCTD) at NCI identifies the most promising areas of science and technology for development of better diagnostic and therapeutic interventions for patients with cancer. DCTD takes prospective detection and treatment leads, facilitates their paths to clinical application, and expedites the initial and subsequent large-scale testing of new agents and interventions in patients. After these diagnostic and therapeutic interventions are adopted in the healthcare community, DCCPS then monitors the dissemination, quality, and outcomes of these diagnostic and treatment interventions in various populations. DCCPS also has responsibility for developing detailed estimates of and determinants of the cost of cancer prevention, screening, treatment and follow-up services, as well as estimating the costs of cancer treatment for patients in clinical trials.



# SECTION 5: QUALITY OF CARE, CANCER OUTCOMES, AND QUALITY OF LIFE

## MEETING THE CHALLENGE

Once almost uniformly fatal, cancer has become a curable disease for many people and a chronic condition for many others. Cancer care thus spans many years, making the quality of cancer care as well as the quality of life of those living with a history of cancer and those caring for them a major national concern; the outcomes of cancer treatment now affect nearly 12 million cancer survivors in the United States. The goal of initiatives related to the quality of cancer care and cancer survivorship is to improve survival and health-related quality of life for individuals with cancer. To accomplish this goal, NCI sponsors research to enhance the quality of care across the cancer control continuum (from risk assessment and preventive care, to screening, diagnosis, and treatment, through follow-up care and end-of-life care) and improve the lives of survivors and their caregivers, as well

as provides leadership that emphasizes substantive collaborations with DHHS agencies and nongovernmental organizations. Although the ultimate goal of eliminating cancer continues to be our long-term commitment, the capacity to dramatically reduce the suffering caused by cancer is within our immediate grasp. NCI leads the nation in championing research on the health and functioning of individuals with cancer during and after treatment.

## SCIENTIFIC ACCOMPLISHMENTS FROM NCI'S INVESTMENT

### COSTS OF CANCER CARE

Advances in cancer screening, diagnosis, and treatment have led to a 75% increase in the overall costs of cancer between 1995 and 2004. As a result, the total economic burden of cancer in 2004 was

## THE EXPECTATION — *From the Cancer Control Review Group Report, 1997*

*A clear mandate must be given to the new DCCPS to conduct research on the identification, prevention, understanding, and treatment of the problems experienced by individuals surviving cancer.*

*NCI needs to clearly embrace health services research related to cancer as part of its mission. Implementing results of cancer control research into health system operations remains a challenge and a topic of critical research.*

*Research is needed on how to best quantify, prevent, and treat physical and psychologic symptoms that result from cancer and its treatments, including fatigue and pain.*

estimated to be \$190 billion. The Health Services and Economics Branch of DCCPS has developed data resources and methods to construct estimates of the economic burden of cancer. Continued monitoring of this burden is necessary, as the costs of cancer are expected to increase as the population ages and more expensive screening, diagnostic, and therapeutic strategies are adopted as standards of care.

The branch has also led efforts to develop detailed estimates and determinants of the cost of cancer care. The cost of cancer care involves not only direct expenditures but also indirect costs, such as lost time and productivity as a result of cancer and its treatment. These time costs have substantial implications for individuals with cancer. In an effort to quantify indirect costs, the branch funded research to estimate the time costs associated with treatment.

In addition, DCCPS has supported several studies to compare the cost of patient care in NCI-sponsored clinical trials with care for nonparticipants. These data are essential to inform ongoing policy debates about the financial coverage by public and private health insurance plans of care received in cancer clinical trials.

#### **DIRECT ECONOMIC COST OF CANCER TREATMENT REPRESENTS SUBSTANTIAL HEALTH CARE BURDEN**

##### **Challenge**

An understanding of the overall impact of the economic burden of cancer required valid and reliable estimates of the economic cost of cancer treatment according to specific cancer sites, stages of diagnosis, and phases of treatment.

These estimates were also essential for conducting cost-effectiveness studies on cancer prevention, screening, treatment, and follow-up care.

##### **Response**

DCCPS staff and extramural researchers developed standard and consistent methods for defining phases of expenditures related to cancer treatment, for applying case-control methods to obtain net costs related to cancer treatment, for constructing estimates of “lifetime” cost, and for addressing statistical issues unique to these types of data. DCCPS also supports the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database, a resource that is integral to determining these kinds of estimates. Cost components were used to construct estimates of the total annual expenditure on cancer treatment by the Medicare program and by the U.S. health care system as a whole.

##### **Progress**

Research showed that cancer is a relatively expensive disease, but expenditures for cancer treatment did not appear to increase as a percentage of all health care expenditures during the 1990s. The total treatment expenditures for each of the four most common cancers were remarkably similar, but the individual costs for other cancers varied widely according to the type of cancer.

Approaches developed by DCCPS investigators and grantees for evaluating the long-term net costs of cancer treatment



from longitudinal data using “phase of treatment” and survival probability techniques have become the standard of practice in the literature on the economics of cancer in recent years. The results of these cost studies have been utilized in numerous cost-effective studies related to cancer prevention, screening, treatment, and follow-up care.

#### SUBSTANTIAL TIME COSTS ARE ASSOCIATED WITH CANCER TREATMENT

##### Challenge

In addition to financial costs, cancer treatment is associated with costs to patients in terms of time, such as the cost for travel to and from medical facilities, time spent waiting for treatment, and time needed for the actual delivery of treatment or other interventions. These costs represent an economic burden for individuals with cancer, their families, and society as a whole. Yet the time-related costs were unknown.

##### Response

Building on the SEER-Medicare linked database and using several other national survey resources, researchers constructed

estimates of the time-related costs associated with the treatment of colorectal cancer. The analytical methods used were similar to those used to construct estimates of direct medical expenditures; this allowed the estimates of time costs and direct medical costs to be comparable. Subsequent research detailed time costs associated with care for the 11 most common types of cancer.

##### Progress

Time-related costs associated with cancer treatment represent a substantial proportion of direct medical costs, especially during the initial phase of cancer treatment and during the last year of life, and vary according to tumor site. Patients’ net time associated with cancer care within the first year after diagnosis ranged from 17.8 hours for melanoma to 368.1 hours for ovarian cancer. Applying dollar amounts (for 2002) to time yielded economic costs ranging from \$271 (melanoma) to \$5,605 (ovarian cancer).

These studies to estimate time-related costs in cancer treatment addressed an important gap in research and demonstrated the importance of these costs. The results provide baseline data that can be used to construct more complete estimates of the economic burden of cancer, and the estimates can be used in cost-effectiveness analyses of cancer control interventions. The authoritative Department of Health and Human Services Panel on Cost Effectiveness in Health and Medicine recommended that time-related costs be considered in all estimates of the economic burden of disease and in cost-effectiveness analyses.







### COST OF TREATMENT FOR PATIENTS IN NCI-SPONSORED CLINICAL TRIALS NOT SUBSTANTIALLY GREATER

#### Challenge

Participants in NCI-sponsored cancer treatment clinical trials frequently found it difficult to obtain health insurance coverage for treatment costs not directly related to the experimental aspects of the trial. Health insurance agencies often sought to exempt themselves from covering treatment in a clinical trial by deeming it “experimental.”

#### Response

DCCPS staff helped design and sponsor several small pilot studies to evaluate the cost of patient care in clinical trials and served as consultants on a full-scale study conducted for NIH by the RAND Corporation. In these studies, the cost of cancer treatment borne by health care insurers for participants in NCI-sponsored clinical trials was compared with the cost of treatment for matched patients with similar characteristics and cancer diagnoses who were not participating in clinical trials.

#### Progress

In all of these studies, the cost of treatment for participants in phase II or III cancer clinical trials was not substantially greater than for patients who did not participate in clinical trials. The results

implicating that denial of health insurance coverage is not based on sound economic evidence informed a policy change by the Centers for Medicare and Medicaid Services (CMS) that enables patients with cancer to participate in approved NCI-sponsored clinical trials without sacrificing the health care coverage benefits of Medicare and Medicaid.

### QUALITY OF CANCER CARE

Despite the significant advances in cancer research over the past decade, many patients with cancer do not receive optimum care. The need to enhance the quality of cancer care in the U.S. received heightened attention in the late 1990s and early 2000s with two reports, the National Cancer Policy Board’s *Ensuring Quality Cancer Care*, and the President’s Cancer Panel’s *Voices of a Broken System: Real People Real Problems*. Both reports documented a wide gap between optimum cancer care and care actually delivered. DCCPS embarked on several important initiatives to respond to the findings of these reports.

The complexity of research on the quality of cancer care requires methods to enhance the available data in traditional databases and cancer registries. DCCPS-funded studies addressed this issue, providing more comprehensive sources of data for the measurement of quality.



One measure of quality is the level of adherence to evidence-based practice guidelines in the community. Studies to assess adherence to guidelines provide insight not only on gaps in the actual delivery of high-quality care but also on whether lack of adherence reflects poor quality of care or lack of consensus on best practices. DCCPS also funded research to determine the relationship between insurance status and guideline-based care. Such research is important for identifying and addressing disparities in health care. Studies were also focused on provider-related variables that affect outcomes of care.

#### DISSEMINATION OF GUIDELINE-BASED CANCER TREATMENT INCREASES

##### Challenge

Historically, the authoritative data source for monitoring trends in cancer in the U.S. had been the NCI SEER cancer registry system (augmented by the Centers for Disease Control and Prevention [CDC] National Program of Cancer Registries). Although SEER provided the best data available on cancer incidence, stage at diagnosis, and survival, it had limited information beyond the first course of cancer treatment. The increasing importance of adjuvant chemotherapy and hormone therapy and a growing interest in patterns and determinants of care in the follow-up and end-of-life phases of cancer called for data resources that allowed for monitoring of these aspects of treatment more effectively.

##### Response

DCCPS has developed several data resources to better monitor the dissemination of guideline-based cancer treat-

ment, understand patterns of care in situations in which a consensus on recommended care is lacking, and document factors related to disparities in care. These resources include the NCI Patterns of Care/Quality of Care (POC/QOC) program, which conducts annual studies that augment routine SEER data collection; the SEER-Medicare linked database, which makes it possible to conduct longitudinal studies of cancer care within the Medicare population; and the HMO Cancer Research Network, which enables researchers to carry out studies within a network of large integrated health care delivery systems.

##### Progress

Evaluation of data showed that the dissemination of guideline-based cancer treatment has increased, although with apparent disparities with respect to patient age at the time of diagnosis (for breast, colorectal, and ovarian cancers), race (for lung and prostate cancers), and type of health insurance (especially for black patients). In addition, some aspects of recommended cancer treatment appeared to be less than fully implemented in the community setting. Factors such as provider volume and referral practices may be associated with appropriate processes and outcomes of care.

The new data sources developed will allow for more comprehensive evaluation of care patterns and determinants of high-quality care. The findings regarding the delivery of care according to guidelines point to specific areas in need of improvement and thus help narrow gaps in the quality of cancer care across populations and settings.

## HEALTH INSURANCE AND RECEIPT OF GUIDELINE-BASED CANCER CARE

### Challenge

A substantial body of literature provided evidence of an association between health insurance status and access to cancer screening. Individuals without health insurance or with only Medicaid were considerably less likely to receive recommended cancer screening services. This challenge was further compounded by the fact that, even when screening tests were available to low-income individuals through community health centers, access to follow-up diagnostic or treatment services was not possible because of high costs.

### Response

DCCPS researchers analyzed data from the POC/QOC program to investigate the association between insurance status (i.e., private insurance, Medicaid or Medicare only, or no insurance) and treatment for 10 common cancers provided according to established evidence-based treatment guidelines. The study was based on a sample of more than 7,000 patients in whom cancer was diagnosed between 1995 and 1999 and who were evaluated in the POC/QOC program.

### Progress

Health insurance status was found to be a robust factor in explaining the receipt of guideline-based cancer treatment for some groups of patients. The findings also suggested that health insurance alone does not explain a large proportion of the discrepancy between observed patterns of care and treatment according to evidence-based guidelines. The results of this research can be used to inform CMS and other third-party payers regarding the coverage needs of individuals with cancer.

## PHYSICIAN AND HOSPITAL VOLUMES ARE FACTORS IN PATIENT OUTCOMES

### Challenge

An association between hospital volume and/or physician volume and patient outcomes had been documented in numerous studies, but the specific types and components of care that result in improved outcomes had not been well understood.

### Response

DCCPS supported several studies that enhanced the understanding of how hospital and physician volume are related to patient outcomes associated with a variety of cancers.

### Progress

The results of studies demonstrated consistently lower rates of morbidity and 30-day mortality for complex operative procedures (such as pancreatic resection or removal of the esophagus) when the surgery was done at a high-volume hospital (a facility at which a large number of a specific procedure is done). In addition, physician volume was a factor in patient outcomes, with better outcomes associated with radical prostatectomy performed by high-volume physicians. It



is important to distinguish between hospital and provider volume and to recognize that additional factors, such as specialized training or specific procedures and practices, may explain substantial variation within a given volume category.

Determining patient outcomes associated with provider-related factors establishes a platform for evaluating specific indicators of high-quality care. Findings of such research also help to identify deficiencies in health care providers and settings and enable individuals with cancer, physicians, and third-party payers to make better informed choices about cancer care.

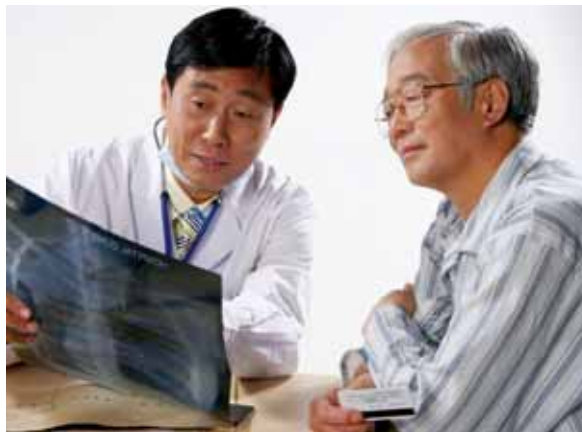
#### QUALITY OF CARE RESEARCH COLLABORATION WITH FEDERAL HEALTH CARE DELIVERY PARTNERS

##### Challenge

The National Cancer Policy Board report, *Ensuring Quality Cancer Care*, documented the “ad hoc and fragmented cancer care system” in the U.S., noting that the system “does not ensure access to care, lacks coordination, and is inefficient in its use of resources.” The report emphasized problems with underuse, overuse, and misuse of existing interventions.

##### Response

NCI established the Quality of Cancer Care Committee (QCCC) in 2000 to strengthen collaborative relationships with federal agencies and private organizations to ensure that cancer care decisions are guided by the best available scientific evidence. Members of the QCCC include federal agencies that deliver, pay for, regulate, or conduct research on cancer care delivery. As a



result of the committee, NCI has initiated cooperative research projects with several agencies, including the Agency for Healthcare Research and Quality, CDC, CMS, Health Resources and Services Administration, the Indian Health Service, National Center for Health Statistics, and the Veterans Administration (VA). One major QCCC project with the VA, The Colorectal Cancer Quality Enhancement Research Initiative (CRC QUERI), demonstrated successful application of evidence to guide federal agency decision-making. CRC QUERI was developed to promote the translation of research discoveries and innovations into patient care and make systems improvements in order to reduce the incidence, late detection, suffering, and mortality from colorectal cancers among veterans.

##### Progress

The initial CRC QUERI projects provided foundational baseline and pilot data on the environmental, organizational, practice, and patient-level predictors of colorectal cancer screening performance among VA medical centers nationwide. Practice-level factors such as facility size and level of primary care practice autonomy and resource sufficiency, as well as



patient-level factors such as income and age were all found to be associated with increased rates of colorectal cancer screening. These data spawned several new initiatives, including projects to develop a Cancer Care Quality Measurement System that will provide data on the quality of colorectal cancer care in the VA; efforts to design guidelines, interventions, and quality indicators that encourage screening healthy older veterans, who are often underscreened; studies to test the use of Home Telehealth Reminders to improve colonoscopic preparation and adherence; and projects to implement a colorectal cancer screening event notification system intervention (CRC-ENS) to improve complete evaluation of patients with positive findings on fecal occult blood testing at four selected VA Medical Centers.

The VA is now using this foundation to set up surveillance and intervention systems to guide cancer care decision-making on a system-wide basis. In addition, QUERI investigators are assembling examples, tools, and templates associated with quality improvement efforts that were initiated by the teams. These resources will be incorporated into a VA web site, and outcomes data will be extracted from electronic medical records and further analyzed.

## ENHANCED CANCER REGISTRIES ALLOW ASSESSMENT OF QUALITY OF CANCER CARE

### Challenge

Many studies of the quality of cancer care had lacked broadly representative patient cohorts or had been limited to patients with Medicare coverage. The federal and state governments invested substantial resources in population-based registries for cancer surveillance, but concerns were raised about the accuracy of adjuvant treatment data in these registries. Furthermore, little was known about patients' views of the quality of their cancer care.

### Response

Through DCCPS grant funding, a study was done to identify data on patients diagnosed with colorectal cancer during 1994 through 2000 whose information was included in the California Cancer Registry and regional registries in northern California. Physicians in northern California were surveyed to augment registry data on adjuvant therapies. In addition, to aid in the assessment of variations in colorectal cancer surgery and survival, statewide cancer registry data were analyzed and nearly 1,500 patients were surveyed eight months after diagnosis to evaluate their experience with care.





### Progress

Evaluation of data showed that adjusted rates of chemotherapy varied significantly among individual hospitals and that use of chemotherapy and radiation therapy varied according to demographic variables (e.g., age, race, and marital status). In addition, black, Hispanic, Asian/Pacific Islander, and non-English-speaking white patients reported significantly lower quality of cancer care than English-speaking white patients. For all racial/ethnic groups, effective coordination of care was the most important aspect of care associated with higher ratings of overall quality of care.

By enhancing population-based cancer registries with improved statistical methods and obtaining additional data on outpatient treatments and patients' experiences with care, these registries can be used more effectively to monitor and improve the quality of cancer care.

### ADVERSE DRUG EVENTS AND REPORTS (RADAR)

#### Challenge

A growing body of evidence indicated that medical errors are a major source of death and disability in the U.S. health care system. A report by the Institute of Medicine, *To Err is Human*, documented almost 100,000 deaths annually as a result of medical errors in health care delivery. The report called for the need to develop surveillance systems that can be used to identify errors and drive quality improvement efforts to reduce their occurrence.

#### Response

The Research on Adverse Drug events And Reports (RADAR) project is a DCCPS-funded research initiative to create and disseminate safety reports for serious adverse drug reactions (sADRs) and to identify barriers to identification and reporting of these clinical events.

#### Progress

RADAR investigators identified key barriers to timely and efficiently identify adverse drug reactions and to comprehensively report these findings.





In particular, they identified quality concerns with MedWatch reports (the U.S. Food and Drug Administration's [FDA's] primary source of adverse event reports) and poor quality of dissemination of adverse event findings from the FDA and the pharmaceutical sponsor. The researchers found that RADAR sADR identification and dissemination efforts can be as rapid as one to two years after FDA approval, in contrast to the seven years generally seen with safety efforts from the FDA and pharmaceutical sponsors.

The RADAR investigators developed a well-coordinated system to accurately compile case report information on sADRs and to establish milestones associated with identification and reporting of the relevant ADR information. This system allows the investigators to amass pertinent sADR information from a diverse set of data sources in order to identify and report sADRs in a timely and thorough manner. Data sources include MedWatch; pharmaceutical suppliers; researchers at centers with extensive experience with cancer drugs; investigators involved with the cooperative oncology groups; Dear Doctor letters distributed in the United States, Europe, Canada, and Australia; abstracts presented at national and international medical conferences; and peer-reviewed journal articles.

As noted in perspectives pieces in the lay literature and in the peer-reviewed literature, and from feedback from patients, their family members, newspaper writers, FDA officials, employees of *Consumer Reports* magazine, and academic pharmacovigilance investigators, the RADAR project has developed into an important adjunct to the current pharmaceutical drug and device safety system.

## OUTCOMES OF CANCER CARE

Although traditional biomedical endpoints, especially survival and disease-free survival, remain of central importance in cancer decision-making, outcome measures that reflect the perspective of the individual with cancer are of increasing interest to researchers and policy makers. In an effort to better understand the affect of cancer treatments on quality-of-life issues, DCCPS funded research designed to evaluate the outcomes associated with common cancers.

One outcome that has been understudied is the effect of cancer and its treatment on an individual's ability to work and the resultant economic impact. Understanding the range of labor market effects of cancer is particularly important as screening—and subsequent diagnosis and treatment—is being carried out on a younger population. In addition, with individuals

living longer and retirement age being pushed further out, the impact of cancer on economic productivity is also growing in importance. The economic impact of cancer is a key element that policy makers should consider when designing and evaluating such policies as early detection programs, medical leave from employment, and portability of insurance.

#### KNOWLEDGE OF PATIENT-CENTERED OUTCOMES FOLLOWING TREATMENT FOR PROSTATE CANCER INCREASES

##### Challenge

Quality of life was particularly relevant to men with prostate cancer because of the prolonged survivorship phase for most men diagnosed with the disease. Before the mid-1990s, little was known about how the various treatment options for prostate cancer (e.g., radiation therapy, radical prostatectomy, and hormone therapies) affected quality of life. Subsequently, researchers began to realize that these treatments varied in their effects on urinary, bowel, and sexual functions.

##### Response

The Prostate Cancer Outcomes Study (PCOS) was initiated to evaluate the impact of treatments for primary prostate cancer on patients' quality of life. PCOS was a collaboration with six cancer registries that are part of NCI's SEER Program to collect information directly from 3,500 men in whom prostate cancer was diagnosed from 1994 through 1995. One of the unique features of this study is that the participants represented a large community-based group of patients with diverse racial/ethnic backgrounds who were treated in a broad range of health care settings.

##### Progress

PCOS was the first systematic evaluation of health-related quality-of-life issues for patients with prostate cancer conducted in diverse health care settings and provided a model for subsequent observational cohort studies of individuals with other cancers. The PCOS posted the comprehensive data on health outcomes of various prostate cancer treatments on the NCI PDQ web site, providing valuable information to men and their families as well as physicians. Men who must decide on treatment for prostate cancer can now consider the unique and significant risks associated with different treatment options and make more informed decisions based on quality-of-life issues that are important to them.

#### LABOR MARKET OUTCOMES OF CANCER SURVIVORS STUDY EXPLORES EFFECT OF CANCER ON WORK-RELATED ISSUES

##### Challenge

The national emphasis on screening for the early detection of cancer was targeted to the working-age population, causing many of these individuals to bear the consequences of cancer during their working years when they may have otherwise lived for some time without knowledge or effects of the disease. For most people diagnosed with cancer, work is a financial necessity, providing both income and health insurance and, for many, a vital source of self-esteem and social support. Working individuals often faced considerable trade-offs between work and treatment, but the impact of cancer and its treatment on employment had not been evaluated or quantified.



### Response

Through the DCCPS program announcement, “Economic Studies in Cancer Prevention, Screening, and Care,” research grants were awarded to better understand the employment experience of individuals diagnosed with cancer. One funded study, the Labor Market Outcomes of Cancer Survivors study, was designed to evaluate the employment status and weekly hours worked, absenteeism, disability, health insurance status, and employer accommodation and discrimination related to individuals with breast or prostate cancer.

### Progress

The findings of the Labor Market Outcomes of Cancer Survivors study provided insight into the effects of cancer on the ability to work and the economic consequences of a cancer diagnosis. Return to work should be considered as a component of quality-of-life issues, and a discussion of how cancer treatments affect employment may help patients and physicians make more informed choices among treatment options. This information may also help identify strategies that employers can use to ensure that valued employees affected by cancer remain in the workforce.

## DEVELOPMENT OF METHODS TO MEASURE OUTCOMES ENHANCES RESEARCH ON QUALITY OF LIFE

### Challenge

Patient-reported outcome measures such as health-related quality of life, perceptions of and satisfaction with care, and the economic impact of cancer were of particular importance to individuals with cancer, as well as their families, health care providers, policy makers, payers, and regulators. For cancer outcomes research to achieve its potential to inform decision-making, measures had to be scientifically sound and regarded as meaningful and useful by these stakeholders. However, these measures posed significant methodologic challenges.

### Response

In 2001, DCCPS established the Cancer Outcomes Measurement Working Group (COMWG), comprising 35 experts drawn from academia, government, industry, and the cancer patient and survivorship communities. Most COMWG members were cancer researchers, selected from the fields of medicine, nursing, psychology, and social work. Members also included experts in economics, biostatistics, psychometrics, and health services research. The goal of the group was to assess the state of the science in cancer outcomes measurement and to identify a research agenda in this area. The primary focus was patient-reported outcome measures, and the majority of the research to date focused on the assessment of health-related quality of life.

### Progress

Investigators found that assessment of health-related quality of life is feasible in a research context, using questionnaires





that meet established criteria for reliability and validity. In addition, methodologic developments, especially the application of item response theory modeling to item banking and computer-adaptive testing, improves precision, efficiency, and comparability in measurement. Use of Bayesian statistical modeling may be effective for integrating outcome results from clinical trials and nonexperimental studies across the cancer control continuum.

The quality and quantity of health-related quality-of-life research has increased substantially over the past decade. NCI and a host of other federal agencies and private cancer organizations now emphasize the importance of collecting data on and incorporating the findings of patient-reported outcomes into the decision-making process to enhance understanding and treatment choices. In addition, the importance of this information in guiding the delivery of high-quality cancer care across the cancer control continuum is now recognized. The findings and recommendations of the COMWG are laying the groundwork for important future investi-

gations, including prospectively designed studies to examine the strengths and limitations of patient-reported outcomes measures and in-depth investigations (including case studies) of the roles of such measures in clinical trials and in real-world decision-making.

## QUALITY OF LIFE FOR CANCER SURVIVORS

In the absence of other competing causes of death, an estimated 66% of adults with cancer can expect to be alive five years after diagnosis. For individuals diagnosed with cancer during childhood (less than 15 years old), five-year survival is now estimated at almost 80%. As the number of survivors and the length of survival expand, long-term health issues specific to cancer survival are rapidly emerging as a public health concern because of the potential for both persistent and late occurring adverse effects of cancer and its treatment. Since 2003, five major reports have been released documenting the need for more research addressing the challenges of cancer survivorship,



two from the Institute of Medicine (*Childhood Cancer Survivorship: Improving Care and Quality of Life* and *From Cancer Patient to Cancer Survivor: Lost in Transition*), two led by the President's Cancer Panel (*Living Beyond Cancer: Finding a New Balance* and *Assessing Progress, Advancing Change*), and one by the Lance Armstrong Foundation in collaboration with CDC (*A National Action Plan for Cancer Survivorship to Advance Public Health Strategies*). The Office of Cancer Survivorship (OCS) in DCCPS has led efforts to identify cancer's long-term and late effects and enhance the quality of life and lengthen survival for cancer survivors.

Monitoring the consequences of cancer survivorship poses several challenges. These challenges include tracking survivors long-term (particularly individuals who survive beyond five years after diagnosis), understanding the factors that may affect risk for poor health and functioning after cancer, developing tools to measure chronic and late effects of cancer, and fostering the support and training of the next generation of investigators and clinicians invested in addressing survivorship research and care. OCS-supported research is showing that the chronic and late effects of cancer include not only physical conditions but also challenges to psychologic and social functioning. Central themes in funded survivorship research are the identification of these effects and the individuals who are at risk for adverse outcomes and the development and delivery of interventions to prevent or mitigate these effects. Studies on survivors' lifestyle choices and behaviors after cancer treatment is providing insight on the preva-

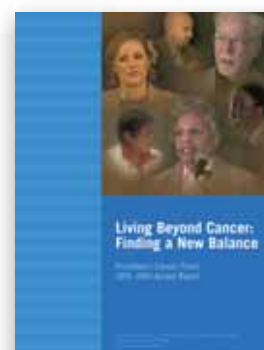
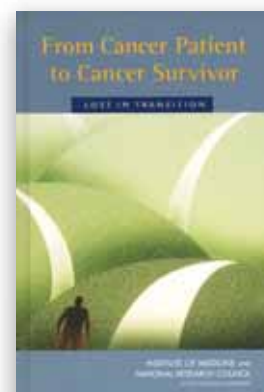
lence of behaviors that affect cancer risk (e.g., physical activity, smoking, alcohol use, sun exposure) and promote well-being (e.g., exercise, vegetable consumption), as well as research on interventions to improve health outcomes after treatment of cancer.

Examination of how best to provide care to survivors after treatment is an additional growing area of attention. Lastly, research has also indicated that cancer affects not just the individual but also the family and that the health of family members and caregivers is important to consider when delivering cancer care and follow-up.

#### LONG-TERM STUDIES INDICATE SUBSTANTIAL LATE EFFECTS OF CANCER AND ITS TREATMENT

##### Challenge

Survival after cancer had improved significantly over the past three decades, mainly as a result of advances in early detection and therapeutic strategies and the widespread use of combined-modality therapy. Late and long-term effects of cancer and its treatment were once thought to exert a deleterious effect primarily among





survivors of childhood cancers, but several studies began to show that late effects were more prevalent, persistent, and serious than expected among survivors of adult cancers.

### Response

Through two initiatives focusing on long-term cancer survivors (those for whom cancer was diagnosed five or more years earlier), DCCPS supported research grants to explore and identify ways to prevent or manage the adverse consequences of cancer and its treatment.

### Progress

Investigators identified a wide range of late and long-term effects of cancer and its treatment. Among childhood cancer survivors, the most frequently occurring medical sequelae were found to be endocrine dysfunction, primary ovarian failure, cardiac dysfunction, neurocognitive deficits, and second cancers. Among survivors of adult cancers, the most

common late effects were found to be second cancers, osteoporosis, obesity, cardiovascular disease, diabetes, and functional decline. Some cancer treatments, such as anthracyclines, trastuzumab, and radiation therapy were found to have cardiotoxic effects, and systemic chemotherapy was associated with risk of fatigue, memory problems, and persistent functional impairment. Some late effects and outcomes were also found to differ according to age and race/ethnicity.

The results of studies to date will facilitate counseling current survivors about their future risk of cardiotoxicity, premature menopause, or other late effects; aid in designing new treatment regimens that decrease the potential for late toxicity; and enhance patient counseling regarding ways to prevent and manage adverse sequelae. These efforts also helped to foster a cadre of investigators committed to examining and identifying the barriers and solutions to studying the long-term impact of cancer on survivors.

## HEALTH BEHAVIORS PLAY IMPORTANT ROLE IN OUTCOMES FOR SURVIVORS

### Challenge

Lifestyle was a known risk factor in the development of some cancers (e.g., smoking and lung cancer) and it influences the development of a variety of other chronic health conditions (e.g., exercise and diabetes and cardiovascular disease). However, the contribution of survivors' health behaviors to risk for subsequent cancer and other cancer-related conditions had not been well-explored.





### Response

Through the support of DCCPS, several studies were initiated to better understand the prevalence of health behaviors among cancer survivors, to develop interventions to improve cancer survivors' lifestyles, and to support several observational studies of individuals with cancer in order to examine the outcomes associated with the adoption of healthy behaviors after diagnosis and treatment. DCCPS-funded research provided national prevalence estimates of the health behaviors of cancer survivors and showed that interventions to promote healthy lifestyles among cancer survivors can be effective.

### Progress

The emerging body of evidence suggests that lifestyle modifications have the potential for improving the long-term health of cancer survivors. At the same time, studies indicate that survivors are interested in learning about behaviors

with the potential to reduce risk of recurrence or manage current health problems. By evaluating the feasibility and effectiveness of such behavioral programs as dietary modification, stress reduction, exercise, and smoking cessation, evidence-based health behavior interventions can be targeted to improve health outcomes, and potentially survival, for cancer survivors. This research is also serving to encourage investigators to examine the role that other health behaviors (e.g., diet, sunscreen use, follow-up screening for second cancers) may have on survivors' outcomes and has led to greater awareness on the part of researchers and clinicians about the need to assess individuals' comorbid status both at the time of diagnosis and across the illness trajectory to better understand the unique contribution of cancer to overall health outcomes.

### FOLLOW-UP SURVEILLANCE FOR CANCER SURVIVORS IS INCONSISTENT

#### Challenge

Clinical guidelines recommended periodic surveillance monitoring for early signs of recurrent or new primary cancers for individuals after treatment of breast or colorectal cancer. Little information was available on how well these guidelines are carried out in community practice.





### Response

DCCPS has developed data resources, such as SEER-Medicare, the Breast Cancer Surveillance Consortium, and the Cancer Research Network, that make it possible to identify large samples of cancer survivors receiving care in the community setting. Using these resources, researchers have been able to identify patterns of underuse and overuse, as well as disparities in the use of follow-up surveillance after treatment for breast or colorectal cancer. Studies conducted using DCCPS-developed resources demonstrated important surveillance patterns and advanced the knowledge about follow-up trends among survivors.

### Progress

The findings of these studies indicated that guidelines for surveillance care are not being consistently followed for a large percentage of cancer survivors. For example, the use of mammography by breast cancer survivors decreased over time, and the use of colorectal cancer surveillance was low among colorectal cancer survivors, especially older black individuals. The determination of particular subgroups of the population of survivors who are more likely to not utilize follow-up surveillance makes it possible to target educational efforts.

In addition, the delivery of follow-up care differed according to the type of physi-

cian who provided follow-up care. A decreasing level of involvement of an oncologist over time was associated with a significant decrease in cancer screening. Survivors who were followed by both a primary care physician and an oncology specialist (shared-care model) were most likely to receive preventive care. This information will help future investigators to examine the impact on health outcomes of different models of post-treatment care delivery (e.g., specialty survivorship clinics, shared-care models, and consultative models).

### FAMILY MEMBERS ARE ALSO AFFECTED BY CANCER IN A LOVED ONE

#### Challenge

With cancer survivors living longer, and cancer becoming a chronic illness for many, family members were increasingly called on to provide key support to loved ones living with a history of cancer. Despite this, limited information existed about the impact of cancer caregiving, either on survivors' well-being or on family members' own health and functioning.

#### Response

OCS has identified research on the impact of cancer on the family as a major focus of survivorship research. The office also provided supplements to several cancer centers to promote research in this area.



Most recently, OCS led efforts to supplement the ongoing Cancer Care Outcomes Research and Surveillance Consortium to permit assessment of 1,637 caregivers providing care to participants in the parent project with lung or colorectal cancer.

### Progress

The findings of studies indicated that cancer can have a substantial effect on the quality of life for parents, children, spouses, siblings, and other family members of individuals with cancer. Findings from this research are serving to

illustrate the reach of cancer's impact beyond the individual and inform efforts to educate and support families in the management of members who become survivors. The cancer experience is being recognized as not just a teachable moment for patients, but also for those with whom they live. Intervening to reduce the stress of caregiving has the potential to improve health outcomes for family members and, by enhancing their efficacy in providing care and maintaining their own health, also that of their care recipients—cancer survivors.



# SECTION 6: MONITORING, REPORTING, AND DISSEMINATING PROGRESS

## MEETING THE CHALLENGE

**T**he U.S. has a national cancer registration system that is structured and funded by collaborative programs operating within the federal, state, and private sectors. Federal programs at NCI and CDC provide more than \$50 million annually to cancer registries in all 50 states, the District of Columbia, and several territories. Data from these registries are available and routinely published on all types of cancers. Cancer surveillance data provide quantitative measures of the burden of cancer and the impact of cancer control interventions in the general population. The success, or lack thereof, of public health efforts to reduce the burden of cancer can be documented



and targeted to population groups in greatest need. Efforts are also ongoing to further integrate the use of cancer surveillance data more directly into cancer control planning efforts, including resource allocation for the purpose of reducing the overall cancer burden.

Significant resources are directed toward research in cancer control, but these advances can be limited by the failure to transfer new, evidence-based findings into the widespread delivery of both individual and population health care. Recognition of this problem has prompted research initiatives to investigate ways to improve the dissemination of new knowledge to a larger target audience, one that includes health care providers, policymakers, and the general public.

## THE EXPECTATION — *From the Cancer Control Review Group Report, 1997*

*SEER coverage needs to be expanded to include several populations not adequately represented: Appalachia; the rural south (with emphasis on African Americans); Native Americans; and Hispanics from Cuban, Puerto Rican, and similar ancestries.*

*Use the SEER expanded data and expertise to produce a timely report card on the cancer burden for broad audiences.*

*Conduct independent methodologic research and engage in collaborative statistical interaction with extramurally funded projects.*





## SCIENTIFIC ACCOMPLISHMENTS FROM NCI'S INVESTMENT

### MONITORING TRENDS ACROSS DIVERSE POPULATIONS

Accurate data on cancer surveillance and trends are essential for monitoring the progress against cancer and for the development of effective screening and prevention programs that target specific populations. The DCCPS Cancer Statistics Branch helps to ensure the collection of cancer-related data through its management of the Surveillance, Epidemiology, and End Results (SEER) Program (<http://seer.cancer.gov/>) and the development of other data collection tools. The SEER Program is the oldest source of comprehensive, population-based cancer information in the U.S. Established in 1973, the database includes information on cancer incidence provided at the state, county, and census tract level. In addition to overseeing the SEER Program, the Surveillance Research Program (SRP) collaborates on the development, implementation, and promotion of data standards for cancer surveillance.



### EXPANSION OF THE SEER PROGRAM

#### Challenge

In 1999, the first two recommendations of the NCI Director's Surveillance Implementation Group, as follow-up to the independent Cancer Control Review Group (1996–1997), were to expand the scope of surveillance research through additional data collection and the development of methods development and to improve how well estimates represent the actual cancer burden.

#### Response

In 2001, the SEER Program expanded its geographic coverage to include Kentucky and remaining counties in California, New Jersey, and Louisiana. With this additional data, the SEER Program increased its coverage from 14% of the U.S. population (in 1998) to approximately 26% of the population. SEER data represent 23% to 71% of racial/ethnic populations (Table).





RACIAL/ETHNIC POPULATION	REPRESENTATION IN SEER (%)
WHITE	23
BLACK	23
HISPANIC	40
AMERICAN INDIAN/ALASKA NATIVE	42
ASIAN	53
CHINESE	53
FILIPINO	69
NATIVE HAWAIIAN/PACIFIC ISLANDER	70
JAPANESE	71

### REPRESENTATION OF RACIAL/ETHNIC POPULATIONS IN SURVEILLANCE, EPIDEMIOLOGY AND END RESULTS (SEER) PROGRAM

To enrich the analysis of cancer rates and trends, SEER has been linked to other data sources, such as the census and Medicare databases, Social Security files, the National Death Index, and motor vehicle registration files. SEER is also being linked to the Indian Health Service database to improve the accuracy of cancer rates reported for the American Indian/Alaska Native population.

### Progress

The collaborative research conducted with SEER data has allowed researchers to better understand the impact of risk factor reduction and prevention, screening, and treatment on trends in cancer death and incidence rates. In 1998, SEER and its cancer surveillance partners documented the first sustained decline in cancer-related mortality since the 1930s.

In 2007, the 10th annual report from these organizations showed that cancer-related deaths decreased, on average, 2.1% per year from 2002 through 2004, nearly twice the annual decrease of 1.1% per year from 1993 through 2002.

The number of data elements collected in SEER is more comprehensive than for any other national cancer surveillance system. SEER includes data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status. A repository of tissue speci-



mens that would otherwise be discarded after a certain time period is being piloted in several SEER registries. Collection of biomarker information has also been initiated.

In the area of bioinformatics, SEER has implemented two new systems: E-Path, which captures data electronically from laboratory health records, and the new SEER data management system to bring together data collected in different formats. The latter has been implemented in three registries, with preparations for a fourth nearly completed. Both systems will provide further cost savings as they continue to be implemented in more SEER registries. These systems were developed to improve the exchange of information while maintaining the strict privacy and security practices throughout.

SRP also has developed a variety of statistical software programs, computer applications, and web-based tools to enhance researchers' abilities to analyze surveillance data, monitor trends, and make projections on the national and local levels. SRP works with the North American Association of Central Cancer Registries to guide all state registries in achieving data content and compatibility acceptable for pooling data and improving national estimates. Also, State Cancer Profiles, a new web-based tool for public health officials and policymakers, provides a user-friendly interface for finding cancer statistics for specific states and counties.

## GEOGRAPHIC INFORMATION SYSTEMS

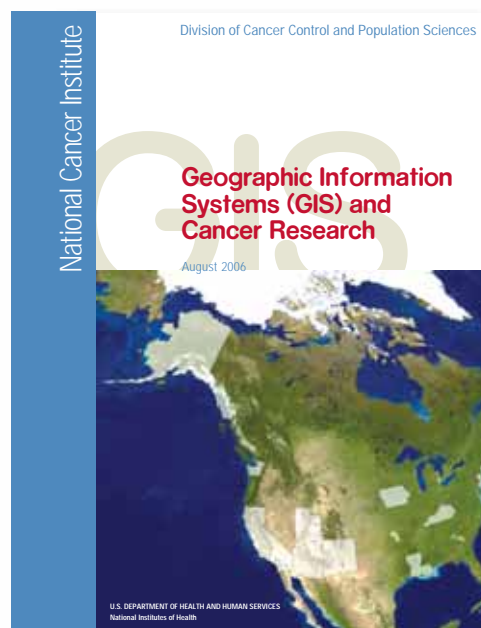
### Challenge

More than 30 years ago, it was recognized that cancer rates vary by geographic location in the U.S. The ability to evaluate

geographic patterns of cancer would allow researchers to identify causes of cancer in local areas and to study the impact of personal behavior and community characteristics on health care outcomes. As a result, cancer prevention activities could be targeted to where they were needed most.

### Response

SRP actively pursued research involving geographic information systems (GIS) for the statistical analysis of spatial and temporal patterns of cancer and data visualization (<http://gis.cancer.gov/nci/>). SRP researchers developed statistical methods for the analysis, display, and web-based communication of georeferenced cancer data. Their statistical models provided a means for identifying significant associations between potential cancer risk factors and cancer incidence, mortality, prevalence, and other cancer outcomes. Spatial models further take into account the similarity of cancer rates in neighboring places. SRP also helps to coordinate extramural geographic-based research in cancer control and



epidemiology through grants that support the use of GIS in cancer research and the development of methodologies to accomplish this research.

### Progress

With GIS, NCI scientists were able to characterize associations between cancer incidence and mortality, sociodemographics, and lifestyle factors by county, using these models to provide an estimated number of new cancer cases by state and county for combinations of cancer site, gender, age, and year. The results of research with GIS will enable researchers to determine better estimates of cancer rates in areas with small populations and to estimate the cancer burden in locations without a cancer registry. The continued improvements in computer technology will make possible more powerful geovisualization tools for exploring and displaying complex layers of geographic information. Reports on the application of GIS include the NCI monograph, *US Predicted Cancer Incidence, 1999: Complete Maps by County and State from Spatial Projection Models*, for which the results were computed by a spatial projection model that predicts the number of cases in each county based on the sociodemographic and lifestyle profile for that county. The purpose was to present, for the first time, complete county and state maps and tables of rates and case counts for 1999 estimated by these new statistical models. From a national perspective, the maps included in the report allow examination of the geographic distribution of cancer incidence across the country and of the magnitude of differences among states. Estimates of the number of new cancer cases and rates expected in an area are

useful for cancer surveillance, cancer control, health resource planning, and quality control activities.

### DEVELOPING LOCAL-LEVEL SURVEILLANCE

#### Challenge

National-level surveillance did not provide data on discrete racial/ethnic populations or specific local regions, such as rural and urban areas. These populations and settings were associated with diverse findings in SEER, the Medicare database, and other information systems. The Surveillance Implementation Group recommended that DCCPS collect regional, state, and local data to help discover reasons for such differences. Subsequent federal reports reiterated the need for comparable and routine population-based information systems at these levels.

#### Response

DCCPS took a leadership role in working with the University of California-Los Angeles Center for Health Policy Research to develop the California Health Interview Survey (CHIS) in 2001. The biennial telephone survey provides population-based, standardized health-related data from households selected from all 58 counties in the state of California.

Because California has the nation's most racially, ethnically, and linguistically diverse population, CHIS provides much needed data on the health and health care needs of such minority groups as black, Latino, Hispanic, American Indian/Alaska Native, and Asian/Pacific Islander populations. Results from this survey are widely disseminated through a





user-friendly computer program (AskCHIS) and public use data files. In addition, descriptions and analyses of CHIS data are provided in various publications (e.g., fact sheets, briefs, and monographs) that are routinely distributed to county public health offices and state legislators.

SRP made additional efforts to improve data on American Indians and Alaska Natives. The problem of scarcity of accurate data on cancer incidence, treatment, and survival trends for American Indians was prevalent in Oklahoma, where, in partnership with the Cherokee Nation of Oklahoma, NCI funds a pilot cancer registry with the goal of building an infrastructure that will be able to meet the SEER standards in case finding, patient follow-up, data processing, data reporting, and quality assurance. The Northwest Tribal Registry Project was developed in 1999 by a tribally operated program located at the Northwest Portland Area Indian Health Board in Portland, Oregon.

## Progress

CHIS has proven to be enormously successful in obtaining local health information and providing data to address health disparities. DCCPS has continued to serve in an advisory capacity for the subsequent surveys. The use of CHIS has enabled the collection of data on several populations for which data had previously been limited, especially the Asian, Native Hawaiian/Pacific Islander, and American Indian/Alaska Native populations. These data have demonstrated trends that had been previously unknown; for example, cancer screening rates within the Asian population were lower than rates in other racial/ethnic minority groups, regardless of health insurance coverage, income, or education. In addition, CHIS data on individuals are geocoded and can be linked with other data systems to further explore cancer trends. In one study in which CHIS was linked with pollution data, researchers found that asthma was more likely to develop in children who lived in homes near freeways. Because of the survey's success, other states have expressed inter-





est in developing statewide local health information systems.

The Alaska Native Tumor Registry became a full member of the SEER Program in 1999. Since then, the registry has completed several reports: its first survival analysis, *Alaska Native Cancer Survival Report*, which was distributed statewide to medical providers, tribal health board members, and key tribal personnel; an update of cancer incidence for Alaska Natives statewide and by Service Unit; and an overall report, *Cancer in Alaska Natives, 1969–2003*. Both the Cherokee Nation Cancer Registry and the Northwest Tribal Registry Project have collected and analyzed several years' worth of cancer data.

## ENSURING SURVEILLANCE ACCURACY

Many factors can have a substantial influence on the accuracy and validity of data collected on cancer incidence and trends. SRP has developed several biostatistical methods and models for confirming the accuracy of surveillance data and for decreasing the potential for measurement errors in research. In addition, qualitative methods were developed to help obtain more accurate self-reports of health behaviors.

Models developed within the program have provided ways to adjust for report-

ing time delays, helping to improve the timely publication of cancer-related data. In addition, SRP encourages and supports research to evaluate the validity of instruments to collect data in national health surveys, as studies have indicated that these instruments do not always capture relevant data accurately. An understanding of the nature and extent of measurement errors in survey instruments is critical for interpreting findings from epidemiologic and monitoring research.

Because of its mission to monitor the differential burden of cancer among Americans, DCCPS also supports and conducts research to improve data systems to advance the understanding of health disparities, particularly the complex factors that are associated with or mitigate differences in health status or outcome.

### METHODS: CANCER INCIDENCE RATES ADJUSTED FOR REPORTING DELAY

#### Challenge

Due to the complexities of collecting cancer data, NCI allowed a delay of 22 months between the end of the diagnosis year and the deadline by which cancer registries must report the information to NCI. The cases for the most recent diagnosis year were, in general, about 4% lower than the total number of cancers that were eventually submitted for that year. This was an important issue in analyzing and reporting trends in cancer rates.

#### Response

In one of the most important statistical advances of the last decade, DCCPS researchers developed models to adjust the current case count for anticipated



future corrections (both additions and deletions) to the data.

### Progress

The results of modeling demonstrate that adjusting for delay tends to increase cancer incidence rates in more current reporting years. The delay-adjustment factor varies by cancer site, taking into account the current practice for diagnosis and treatment. These adjusted counts and the associated delay model are valuable in more precisely determining current cancer trends. The model is now widely used in trend analysis and has been a major contribution to the timely reporting of cancer data.

### PROJECTION OF CANCER RATES TO THE CURRENT YEAR

#### Challenge

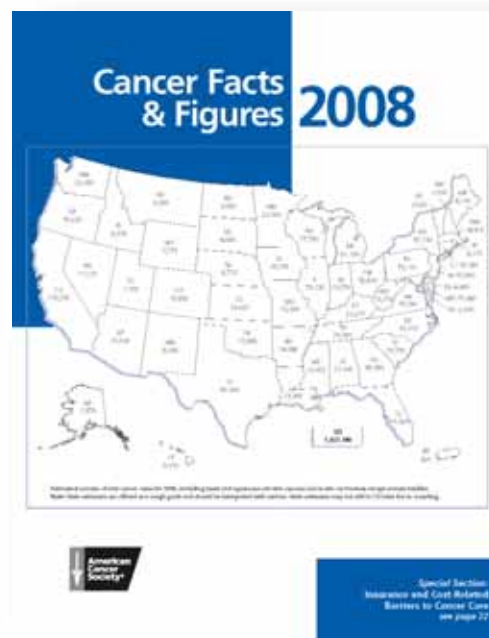
Timely estimates of the number of deaths and new cases of cancer provided important information for cancer control planners, public policy analysts, and state health departments, who need to know the relative burden of different types of cancer for the U.S. as a whole and for individual states. Because the lag in reporting cancer statistics was usually three or four years, there was a need to project the estimates ahead to the current calendar year. In addition, the number of new cases was not reported by all states, creating an additional need to estimate the missing data.

#### Response

DCCPS statisticians developed statistical models to provide estimates for both mortality and incidence for the current calendar year for every state and for the country as a whole.

### Progress

These estimates began to be used by the American Cancer Society (ACS) for their annual *Cancer Facts and Figures* report, which is the most cited cancer publication for current-year cancer rates.



### UNDERSTANDING LEVEL OF ACCULTURATION AS A CORRELATE OF HEALTH BEHAVIORS AND AS A BARRIER TO SURVEILLANCE

#### Challenge

The U.S. population includes vibrant communities of immigrants, spanning a wide range of language, education, and income levels, as well as number of years in this country. Health behaviors change with duration of residence, and the capacity to respond to standardized surveys also changes. Obtaining valid and reliable answers to questions about complex and sensitive aspects of behavior could help to address disparities associated with immigrant populations.



### Response

DCCPS aggressively pursued incorporation of cognitive testing in multiple languages (especially Spanish) and behavior coding (with interviews in Spanish and Korean) as tools for improving standardized survey questions. These efforts involved work by a multidisciplinary team that included a cognitive psychologist, a nutritionist, a psychometrician, and a physical activity researcher. Additionally, this team has carried out a number of projects focusing on the analysis of associations between acculturation and health behaviors and the review of existing tools for assessing acculturation.

### Progress

Level of acculturation is one of the strongest correlates of energy balance-related health behaviors, including levels of physical activity, consumption of fruits and vegetables, and use of tobacco and alcohol. However, less acculturated individuals have trouble defining and interpreting many language constructs used in

questions about acculturation itself, and in questions asking about the frequency of health behaviors. These results suggest that further efforts to match survey tools to the cognitive and cultural aspects of immigrant populations are critical to obtaining valid descriptions of health behaviors in these communities.

### DEVELOPMENT OF QUALITATIVE METHODS IMPROVES CANCER-RELATED SURVEYS AND RESEARCH

#### Challenge

Cancer research that involves the self-reporting of risk factors, such as physical activity, diet, tobacco use, and sun protection, as well as cancer screening behaviors, requires the use of survey questionnaires and measurement instruments that obtain subjective reports from patients and study subjects. It was vital to develop methods for designing instruments that produce reliable and valid data.





### Response

To further the state of the art of the development and testing of self-report measurement instruments, DCCPS championed the establishment of a set of qualitative methods through several means, including the dissemination of best practices of questionnaire design through a downloadable guide; the development of empirical methods for assessing sources of self-report error, especially cognitive interviewing and behavior coding for “product testing” of survey questions to ascertain whether they function as intended; the creation of methods to develop best practices for item translation and production of questionnaire-based items that exhibit cross-cultural equivalence; and the undertaking of computer usability studies, including the development of a web-based system for the automated collection of self-reported 24-hour dietary recall data.

### Progress

The incorporation of qualitative methods—in particular, cognitive interviewing and behavior coding—has become a fixture in DCCPS-supported surveys, such as the National Health Interview Survey and CHIS. For example, these methods were used for the quality assurance test-

ing of translations of the Tobacco Use Supplement to the Current Population Survey (TUS-CPS) into five languages and have enabled local area tobacco control researchers to reach populations that were previously linguistically isolated. Furthermore, recently developed DCCPS protocols for survey translation are now available across a range of epidemiologic surveys carried out by the extramural research community.

### OBJECTIVE MEASURES AND STATISTICAL MODELING ADDRESS A MAJOR SOURCE OF ERROR IN SELF-REPORTED DIET AND PHYSICAL ACTIVITY DATA

#### Challenge

Diet and physical activity are believed to play important roles in the etiology, prevention, and treatment of many chronic diseases, including some types of cancer. A decade ago, epidemiologists relied on self-reports to measure these behaviors, but many investigators expressed concern that such assessments were replete with bias and other types of measurement error.

#### Response

NCI embarked on a program of research using objective dietary and physical activity measures and statistical methods to

investigate bias and measurement errors and to address them in its surveillance and other research activities. One study in this program, the Observing Protein and Energy Nutrition (OPEN) study, was designed to examine dietary measurement error in food frequency questionnaires (FFQs) and 24-hour dietary recalls. This study used double-labeled water and urinary nitrogen as unbiased biomarkers of total energy expenditure and protein intake.

### Progress

The results of the OPEN study showed that measurement error in the FFQ seriously reduced its ability to detect potential associations of absolute protein or energy intake with the relative risk of disease. Measurement error in the 24-hour dietary recall also cast doubt on its use as a reference instrument for validating and calibrating FFQs for nutritional epidemiologic studies.

The OPEN results led to a major shift in the conduct of nutritional epidemiologic studies, with researchers now reconsidering how best to measure diet and with studies involving FFQs now beginning to incorporate corrections for measurement error. NCI supports numerous studies to develop better methods of gathering dietary data, including the development of automated self-administered 24-hour recalls, as previously mentioned. NCI has also developed sophisticated statistical models to estimate usual dietary intakes from limited 24-hour recall data.

More recently, NCI broadened this area of research to include physical activity by introducing accelerometers into the National Health and Nutrition

Examination Study 2003–2006, providing the first-ever national estimates of physical activity with objective data. The inclusion of these devices provided evidence that the prevalence of activity commensurate with current recommendations is much lower than has been suggested from responses on questionnaires.

These findings have obvious implications for public health practice and also for the conduct of future studies. A new standard has been set for measuring physical activity in a comprehensive manner that includes leisure time as well as other types of activity.

In addition to the specific results of these two studies, NCI researchers have demonstrated that it is, in fact, possible to use objective methods to measure dietary and physical activity behaviors. Although dietary biomarkers are available only for a small number of dietary components and are still impractical to include in large studies, they are still of substantial value for assessing the validity of self-reported measures.



## COMBINING SURVEYS FOR IMPROVED ESTIMATES OF RISK FACTORS AND SCREENING RATES

### Challenge

Effective cancer control plans rely on accurate information about risk factors and screening in the target geographic areas. The two major national health surveys that compile information on cancer risk factors and screening behaviors have complementary strengths and weaknesses. Although the potential for combining results from these major surveys had been discussed, it had never been implemented.

### Response

DCCPS scientists initiated and developed a collaborative research team that included statisticians from academia, NCI, and NCHS to derive methods to combine the National Health Interview Survey (NHIS) and the Behavior Risk Factor Surveillance Survey (BRFSS) in order to draw on their complementary strengths.

### Progress

The development of estimates using the combination of these two surveys required the use of complicated statistical models. Over a five-year period of research, two usable estimators emerged from the collaborative efforts. The first, called Model-Assisted, corrects for potential biases by modifying the BRFSS statistical weights to “behave” more like the NHIS weights. The method has been applied using the NHIS public use data files, with geographic identifiers available only at the regional level. The second method, called Model-Based, corrects the bias by modeling the responses directly as a function of the individual and county characteristics of the respondents.

These estimators represent a major step forward in survey research because they correct for the biases and variability of estimates based on data from small areas. The development of a web site for posting county, health service area, and state-level estimates of cancer risk factors and screening behaviors using the new methods has been a collaborative enterprise. The success of this research has enhanced the availability and use of data collected by several agencies, adding important value to the existing national surveys.

## MEASURING CANCER DISPARITIES

### Challenge

The Department of Health and Human Services publication, *Healthy People 2010*, has two overarching goals: to increase the span of healthy life and to eliminate health disparities across the categories of gender, race/ethnicity, education level, income, disability, geographic location, and sexual orientation. Despite the increased attention to social disparities in health, no clear framework existed to define and measure health disparities. This had the potential to create confusion in communicating the extent of cancer-related health disparities and hinder the ability of public health organizations to monitor progress toward the cancer objectives in *Healthy People 2010*.



## Response

In 2006, NCI commissioned the monograph, *Methods for Measuring Cancer Disparities: A Review Using Data Relevant to Healthy People 2010 Cancer-Related Objectives*. This monograph includes a review of indices from a range of disciplines, which are then applied to the measurement of cancer-related health disparities. The methods set forth in the publication provide a new foundation for measuring cancer-related health disparities.

## Progress

Choosing measures of health disparity involves consideration of conceptual, ethical, and methodologic issues. The NCI monograph discusses some of these issues and provides recommendations for a suite of measures that can be used to monitor health disparities in cancer-related health outcomes. Some of the indices reviewed in the monograph were not previously used in public health. As part of a strong evidence base, including illustrative examples, this monograph provides a firmer foundation for policy and program initiatives, including *Healthy People 2010* and other public health initiatives.



To promote the development of research that will generate an evidence base for population-based health policy, this seminal work has been disseminated to a range of constituencies, including health policy researchers and administrators, social epidemiologists focusing on health disparities, and biostatisticians developing methods to measure cancer-related health disparities. This work is on the leading edge because it provides the most comprehensive comparison of measures of cancer-related health disparities available to date. A second monograph describing case studies that apply these measures of health disparity, *Selected Comparisons of Measures of Health Disparities: A Review Using Databases Relevant to Healthy People 2010 Cancer-Related Objectives*, was published in 2007.

## INTERPRETING, PROJECTING, AND DISSEMINATING TRENDS

Cancer incidence trends can be a challenge to interpret as a measure of success because changes in incidence are a function of many factors, including the increased use of screening, the introduction of new diagnostic technologies, and changes in the risk factor profile of the population.

Essential corollaries to the development of cancer surveillance databases and cancer control interventions are the statistical analyses and mathematical modeling that contribute insight into the interpretation of these data. The Statistical Research and Applications Branch conducts and supports research targeted at improving and developing statistical methods and models for use in the analysis and presentation of population-based

cancer statistics, as well as in the broader areas of cancer surveillance and cancer control research. Among the areas of research are the development of new analytic approaches for the presentation and estimation of incidence, survival, mortality, and related cancer statistics; models and methods to project the effect of new cancer control activities; statistical and mathematical modeling that provides a link between data and the assessment of progress in cancer control; and methods to monitor the prevalence of risk factors in the population.

The dissemination of cancer-related data is also an important function of DCCPS. Researchers, clinicians, public health service providers, and policymakers need updated data on national trends throughout the cancer control continuum, from prevention, early detection, and diagnosis through treatment, survivorship, and end-of-life care. The timely dissemination of research findings that will have an impact on outcomes is essential for ensuring that individuals have the potential to take advantage of the most recent advances in risk reduction, screening, diagnosis, and treatment. To address this need, DCCPS

began publishing *Cancer Trends Progress Report* in 2001, a report that is updated every two years. The report, available online (<http://progressreport.cancer.gov>), summarizes the nation's progress against cancer in relation to the targets noted in *Healthy People 2010*. In 2005, the report offered treatment trends data on breast and colorectal cancers and also included enhanced features that enabled readers to select and print specific sections and subsections.

#### ESTIMATING THE PREVALENCE OF SECOND CANCERS IN CANCER SURVIVORS

##### Challenge

The issue of cancer survivorship gained greater importance as clinicians and researchers began to recognize the unique challenges of long-term survivors of cancer. (See Section 5 “*Quality of Care, Cancer Outcomes, and Quality of Life*.”) As more cancer survivors began to live longer, the need arose to determine the prevalence of second cancers in this population.

##### Response

To better understand the demographics of the U.S. population of cancer survivors, the Office of Cancer Survivorship and the Surveillance Research Program worked together to develop survivorship prevalence estimates based on the SEER registry data. This research has been possible through the development of new methods to calculate lifetime prevalence with use of data from younger cancer registries. In a study generated by this research, NCI scientists also were able to describe 10-year prevalence rates for a variety of cancer survivor groups.



### Progress

Studies of more than 50 adult and 18 childhood cancers have shown that there is a 14% increased risk of a subsequent cancer among cancer survivors compared with what would be expected in the general population. In addition, investigators were able to identify which types of cancers were more likely to be followed by a subsequent primary cancer.

Although a sizable portion of multiple cancers in the SEER database represented tumors that occurred in the same or neighboring organ systems, most of the subsequent cancers occurred in diverse organ sites.

Many of the patterns of multiple cancers suggested an effect of shared risk factors (such as use of tobacco and alcohol, nutritional factors, hormones, infections and immunosuppression, and genetic predisposition) or a carcinogenic effect of cancer therapies. One of the most striking findings was that tobacco smoking, excess alcohol intake, or the interaction of the two exposures appeared to account for more than 35% of the excess cancer risk observed in the survivor population.

The estimation of cancer prevalence among cancer survivors highlights the importance of medical follow-up for prevention and early detection of new malignant diseases. A monograph published in 2005, *New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000*, describes and quantifies the risk of a new cancer developing among more than two million cancer survivors, utilizing data from the SEER Program cancer registries.

### DEVELOPMENT OF POPULATION ESTIMATES FOR THE RISK, BENEFIT, AND USE OF CANCER CHEMOPREVENTION AGENTS

#### Challenge

In 1998, results from the Breast Cancer Prevention Trial (BCPT) demonstrated a 49% reduction in the risk of invasive breast cancer and a 50% reduction in the risk of noninvasive breast cancer among women at high risk of breast cancer who were assigned to receive tamoxifen during an average follow-up of four years. Unfortunately, some adverse outcomes were associated with the use of tamoxifen in BCPT, including excess risks of endometrial cancer, pulmonary embolism, stroke, deep vein thrombosis, and cataracts. In order to understand the public health implications of the BCPT results, a full evaluation of the impact of tamoxifen chemoprevention at the population level was needed, with consideration of both the adverse events and the proven benefits for breast cancer risk reduction.

#### Response

Using a benefit/risk tool that weighs the benefits of chemoprevention with tamoxifen against the risks, and nationally representative data from NHIS conducted in 2000, DCCPS investigators were able to estimate the number of U.S. women who would be eligible for chemoprevention with tamoxifen (based on indications approved by the FDA), the number of women who had evidence of a positive benefit/risk index, and the number of women actually taking tamoxifen to reduce their risk of breast cancer.





### Progress

According to the findings of this research, a substantial percentage (15.5%) of women in the U.S. were eligible for chemoprevention with tamoxifen but a much smaller percentage (4.9%) would have an estimated net benefit. Although this latter percentage was low, it corresponded to more than two million women. In contrast, the study estimated that 70,000 women were currently taking tamoxifen to reduce the risk of breast cancer. The investigators further calculated that if all women who had an estimated net benefit for tamoxifen chemoprevention took the drug over the subsequent five years, approximately 28,000 breast cancers would be prevented or deferred during that time.

This study, one of the first of its kind, contributed substantially to the understanding of the current use, risks, and benefits of a new chemoprevention agent at the population level. The findings emphasized the importance of examining the risks and benefits of certain drugs at this level and highlighted the impact that a chemoprevention agent can have on overall cancer burden.

The study garnered a great deal of attention in all the major news outlets, including CNN; has been cited in the scientific literature more than 45 times since it was

first published in 2003; and is now included in the ACS *Cancer Facts and Figures*. The study has paved the way for a similar analysis of another chemoprevention agent, raloxifene, which was shown in the Study on Tamoxifen and Raloxifene trial to perhaps be as effective as tamoxifen at reducing invasive breast cancer in high-risk women, possibly with fewer side effects.

### ESTIMATING SURVIVAL IN THE PRESENCE OF COMORBIDITIES

#### Challenge

Traditionally, relative survival has been the cancer survival measure that is reported. Cancer survival statistics are typically expressed as the proportion of patients alive at some point subsequent to the diagnosis of their cancer. Relative survival is an estimate of the percentage of patients who would be expected to survive the effects of their cancer. Observed survival is the actual percentage of patients still alive at some specified time after diagnosis of cancer. It considers deaths from all causes, cancer or otherwise. Policymakers and advocacy groups

may be interested in death from cancer where the confounding effects of death from other causes are removed (e.g., when comparing survival from cancer for different racial/ethnic groups with very different other-cause mortality). However, individuals with cancer may be interested in both the probability of death from cancer and the probability of death from other causes, with each estimated in the presence of the other.

### Response

SRP researchers developed a measure that estimates the probability that an individual with cancer will die as a result of the cancer, along with the probability that the individual would die of other causes. The measure was added to the SEER\*Stat software for analysis of SEER and other population-based data sets.

### Progress

The development of this measure represents the initial steps to providing patients with clearer estimates of their risk of dying of cancer and to help them better understand their prognosis and evaluate different treatment options. This work has led to ongoing research to estimate survival as a function of comorbid conditions, and software that incorporates survival in the presence of both other-cause mortality and individual comorbidities is currently under development. The data generated by this software can be used by clinicians to communicate the mortality risk of a cancer diagnosis when counseling patients.

## IMPACT AND PUBLIC HEALTH POLICY

Decision-making about population-level cancer control initiative is sometimes difficult, as is evaluating the success of the strategies chosen. DCCPS researchers have worked to develop important tools and resources to help guide clinical and policy decision-making on cancer control. These research initiatives can help to gain a better understanding of cancer control interventions (in prevention, screening, and treatment) on population trends in incidence and mortality. These tools not only help in identifying cancer control strategies that have been effective but can also help in the development of better strategies and in projecting future trends.

Statistical models are required to link upstream factors, such as prevention and early detection, with outcomes, such as cancer incidence and mortality. These models provide a vital feedback loop between national trends in cancer rates and the research advances and cancer control efforts of the nation.



## MODELING THE IMPACT OF CANCER CONTROL INTERVENTIONS ON NATIONAL CANCER TRENDS

### Challenge

Although research had established cancer trends, explanations of the underlying reasons for the trends were lacking. In addition, studies were needed to project the impact of evolving cancer control interventions on future trends.

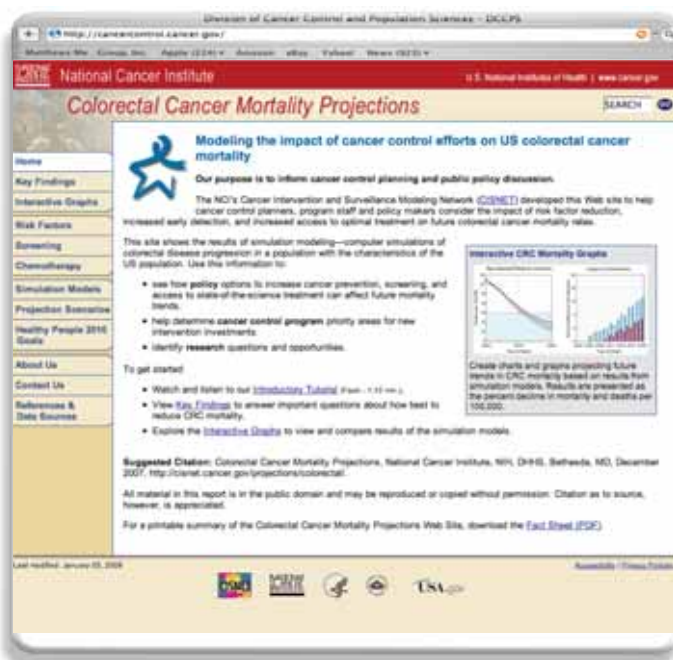
### Response

A consortium of statistical researchers was brought together by NCI to participate in the Cancer Intervention and Surveillance Modeling Network (CISNET). CISNET uses biostatistical modeling to improve the understanding of cancer control interventions in prevention, screening, and treatment. CISNET researchers develop models using data from randomized controlled trials, meta-analyses, observational studies, national surveys, and studies of practice patterns to evaluate the past and potential future impact of clinical and public health interventions.

Currently, CISNET has four groups of teams that focus on breast, prostate, colorectal, and lung cancers. Because of the high incidence of these cancers and the associated mortality, informed decisions regarding effective clinical and public health interventions for these cancers would have an enormous impact.

### Progress

CISNET models have been used to address important questions in cancer control: to project future incidence and mortality rates under various assumptions for risk factors, screening, and treatment; and to carry out cost-effectiveness analyses of competing interventions and thus identify optimal cancer control strategies. For example, the CISNET lung group used modeling at the state level to quantify the impact of tobacco control policies on smoking rates and ultimately mortality. Other models have enabled researchers to compare the relative clinical and economic performance of conventional fecal occult blood tests and newer immunochemical tests for colorectal cancer screening.





The results of studies with these models help the public better understand the risk and benefits of behaviors in terms of cancer outcomes. They also provide a valuable resource for policymakers in determining goals for public health and the best options for allocating limited resources. A new interactive web site allows policymakers to evaluate the impact of alternative cancer control strategies (e.g., risk factor reduction, increased early detection, increased access to optimal treatment) on future colorectal cancer mortality rates (<http://cisnet.cancer.gov/projections/colorectal/>).

#### ESTIMATING THE IMPACT OF MAMMOGRAPHY AND ADJUVANT THERAPY ON U.S. BREAST CANCER-RELATED MORTALITY FROM 1975–2000

##### Challenge

The mortality rate associated with breast cancer began to decline in the early 1990s, and there was scientific debate about the contributions of mammography and adjuvant therapy to this decline. Most researchers expected that adjuvant therapy (both multiagent chemotherapy and hormone therapy) was the primary factor

in the decline because of the persuasive results of clinical trials. However, there was a sharp dispute over whether screening with mammograms contributed to the decline, as the findings of randomized controlled trials had been ambiguous.

##### Response

Seven research teams participating in CISNET collaborated on an analysis to estimate the effect of screening mammography and adjuvant therapy on breast cancer-related mortality. The researchers used a comparative modeling approach to describe the dissemination and usage patterns of mammography and adjuvant therapy that occurred over time in the U.S. The usage patterns were then coupled with seven independent modelers' syntheses of all available information on the benefits of these advances. The project was a unique opportunity to compare a variety of modeling approaches in the context of an important public health question and as a result, it afforded a more comprehensive view than would have been achieved by a single model, as well as a more realistic representation of the uncertainty related to the modeling results.

##### Progress

The results of the research, published in 2005, were definitive in demonstrating that neither screening nor treatment alone could fully explain the decline in mortality in any of the models; in fact, each factor accounted for about half of the historic 24% decline in mortality that occurred between 1990 and 2000.

Because these results reflected the entire U.S. population experience, they shed insight on recent controversies surround-





ing the analysis and interpretation of meta-analyses of mammography screening trials. In addition, as highlighted in a 2006 issue of the *Journal of the National Cancer Institute*, CISNET demonstrated a process for collaborative work and an example of how statistical modeling can play an expanded role in providing input to public health policy and decision-making.

#### RAPID DECLINE IN POSTMENOPAUSAL HORMONE THERAPY USE FOLLOWING RELEASE OF FINDINGS FROM THE WOMEN'S HEALTH INITIATIVE STUDY ON ESTROGEN PLUS PROGESTIN

##### Challenge

It has been estimated that it can take as long as 17 years for results from biomedical research to be taken up by the public and by clinical practice. When the results from large-scale NIH clinical trials indicated that specific drugs influence the risk of cancer, more immediate dissemination of results was needed to ensure better implementation of care that addresses the change in risk.

##### Response

DCCPS increased the capacity to track the use of drugs that may influence cancer risk through its development of

population-based health surveillance systems built within clinical practice systems, such as the Cancer Research Network and the Breast Cancer Surveillance Consortium.

##### Progress

The Women's Health Initiative Study on Estrogen plus Progestin Therapy (WHI EPT) was stopped early because of evidence of an excess risk of invasive breast cancer, coronary heart disease, and other vascular events associated with the hormone therapy. Although NIH had not developed monitoring systems to evaluate the effect of these trial results, the Breast Cancer Surveillance Consortium and the Cancer Research Network had the capacity to examine changes in the use of hormone therapy both before and after the release of the WHI EPT findings. Following the publication of the trial results, the use of hormone therapy decreased dramatically and rapidly across all races and socioeconomic groups; within five months, the use of estrogen and progestin therapy had decreased by 46% and estrogen-only therapy had decreased by 26%. A study within the Cancer Research Network found that every health plan had issued responses in terms of patient and provider education and guidelines within three months of the termination of WHI EPT, and the researchers concluded that this response played a role in the decline in the use of hormone therapy among plan members. In addition, an ancillary study within the Breast Cancer Surveillance Consortium showed that publication of the WHI EPT results was associated with an increase in the volume and content of newspaper coverage.



This research demonstrates that rapid change in practice and health behaviors at the population level is possible following major NIH trials when results are widely publicized and disseminated. The ability to document such changes has major implications in terms of newly emerging policy areas.

#### PROVIDING DATA ON TOBACCO USE AND POLICIES

##### Challenge

The American Stop Smoking Intervention Study for Cancer Prevention (ASSIST), which was established in the late 1980s, required a comprehensive state-level survey to assess important macro-level environmental exposures, salient pieces of the intervention, and the major outcomes. In addition, two independent review groups advised DCCPS in its early days to maintain capacity to track progress in tobacco control on the state level in terms of both individual behavior and environmental influences.

##### Response

NCI partnered with the Census Bureau to conduct TUS-CPS. The CDC Office on Smoking and Health joined as a cospon-

sor in 2001. TUS-CPS is conducted approximately every three years, alternating between a “core” survey and a special topic survey, such as the Tobacco Use Special Cessation Supplement (TUSCS) used in 2003. Data from the surveys are made publicly available by the Census Bureau, with scientific support from NCI and CDC.

##### Progress

The most recent TUS-CPS (2003) provided important information on the overall prevalence of cigarette smoking, the prevalence among subgroups (based on sex, age, geographic location, and racial/ethnic background), the rate of cessation activity, and the percentage of smoke-free environments (workplaces and homes). The findings showed that the overall prevalence of smoking among adults (18 years and older) has declined since 1992, but the rate still exceeds the target of 12% set in *Healthy People 2010*. The prevalence of current smoking was lowest for women, individuals 65 years and older, individuals living in the western part of the U.S., and individuals in the Asian/Pacific Islander and Hispanic populations. Smoking cessation activity or successful cessation was most likely among individuals with at least 16 years of education and least likely among individuals with less than 12 years of education. Attempts to quit were lower among individuals who lived in the south than among individuals who lived in other areas of the U.S.

Data from the study also showed that 77% of the workforce reported working under a smoke-free policy, but the percentage varied widely among states.



The highest percentage of smoke-free workplaces (for both smokers and nonsmokers) was in Delaware. This result was exciting, as Delaware had previously implemented a statewide ban on smoking in indoor workplaces, restaurants, and bars. Approximately 74% of respondents reported that smoking was not allowed in their home.

This survey has been a remarkable resource for research, monitoring, and advocacy for government, extramural scientists, advocates, and those interested in state tobacco control and health disparities research. More than 90 journal articles and reports have been published, including Surgeon General's reports, utilizing the data. TUS-CPS data were instrumental in a DHHS litigation case against the tobacco industry and have also been used by the CISNET team in making predictions about the likelihood of reaching the *Healthy People 2010* goals for lung cancer. It is expected that the data will be a valuable resource in the future for states that need other sources of data as their financial resources further constrain them to monitoring less frequently.

#### PROVIDING METRICS TO ASSESS POLICIES

##### Challenge

Federal, state, and local policies can play a pivotal role in the adoption of healthy behaviors and, as a result, in cancer control. Research was essential for establishing the need for policies, for tracking the population's adherence to policies, and for evaluating the impact of various policies.

##### Response

NCI has provided data and developed measures to assist in formulating and evaluating policies addressing several cancer-



related health behaviors. Together with researchers across the federal government, NCI produced a compendium of articles in which data related to each of the *Dietary Guidelines for Americans* were evaluated; collectively, the guidelines form a statement of federal nutrition policy. The articles provided information on the degree to which the population was meeting each of the recommendations and on the system-level factors that may have an impact on relevant behaviors. In addition, the researchers identified gaps and limitations of the data for addressing critical policy-related questions. A separate analysis, conducted with colleagues at the U.S. Department of Agriculture and Cornell University, quantified the discrepancies between dietary recommendations and current U.S. intakes, at both the individual and aggregate food-supply levels.

NCI also partnered with ACS to implement and evaluate the ASSIST project.

Investigators developed several indices to use in evaluating tobacco control policies at the state level: a Strength of Tobacco Control index (SoTC), an Initial Outcomes Index, and a Media index. SoTC includes information on three major components of state-level tobacco control programs: resources, capacity, and program efforts focused on policy and environmental change.

### Progress

Many of the suggestions generated by the NCI-supported research were incorporated into the latest version of the *Dietary Guidelines for Americans*.

According to the findings, several changes in the population's intake are needed to meet current federal dietary guidance, and these changes would require dramatic shifts in food production. The results of the research provide agriculture policy experts with the data necessary to evaluate projected shifts in commodity supplies that would be needed in order for the population to meet dietary recommendations.

According to the evaluation of the ASSIST project, states with higher SoTC scores had lower rates of tobacco use. Capacity was the strongest of the factors examined, and states that had developed higher levels of capacity had significantly lower rates of tobacco use. Funding alone was a necessary but not sufficient factor for public health outcomes in tobacco control. It was found that a single score – the SoTC—can provide a relative ranking of state tobacco control and serve as an indirect measure for tobacco control program effects at the state level.

## HEALTH COMMUNICATION

At the time when DCCPS was formed, tremendous advances were being made in the field of communication technology. While health care providers were once the sole source of health information, several new sources began to emerge: radio, television, print media, friends and family, and the Internet. The advances in communication technology have enhanced the spread of health informa-

tion, but the multiple sources create a challenge in maintaining high quality and consistency of information. The potential for conveying inaccurate or contradictory health information has been borne out in studies showing that high percentages of the population are misinformed about various cancer-related topics.

The Internet has become a primary source of health information.

Approximately 95 million adults—nearly half of the U.S. population—search online for health information. Cancer is the third most popular health search on the web. However, preferences for sources vary among populations; for example, print media is the preferred source for black individuals, and health professionals are the most trusted source particularly for older individuals and Hispanic individuals. Research is needed to analyze how people use various sources of information and how those sources influence their knowledge and acceptance of healthy living guidelines.

### ESTABLISHING A SYSTEM FOR MONITORING EVOLVING CANCER COMMUNICATION NEEDS

#### Challenge

Learning how to take full advantage of new capabilities in the rapidly evolving field of communication technology during a time of significant advances in cancer had become a public health imperative.

#### Response

To understand the nature of the communication revolution, DCCPS launched the Health Information National Trends Survey (HINTS) in 2001

(<http://hints.cancer.gov/>). The purpose of HINTS is to monitor the ways in which the general population obtains information relevant to cancer control. HINTS provides scientists with a distinct perspective on how changes in communication technology influence the general population's ability to engage in self-protective behaviors in accordance with a cancer control agenda.



### Progress

Researchers found that there are substantial differences between individuals' preferences for information sources and the actual sources used; although survey respondents said they prefer to obtain cancer information from their own physician, most respondents reported that their first actual source of cancer information was the Internet. In addition, the benefits of the new health information revolution did not penetrate equally throughout the population, and there were significant "knowledge gaps" among factions of the

population with regard to what is known about preventing cancer or even where information on cancer can be obtained.

The research conducted by scientists in the HINTS community is changing the way public health professionals, health service administrators, clinical practitioners, and population scientists think about the role of communication in cancer control. These scientists are developing the evidence base for the next generation of communication interventions and will provide the surveillance needed to monitor and improve the interventions over time.

### INTERNET-BASED SEARCH ENGINE FOR HIGH-QUALITY HEALTH INFORMATION

#### Challenge

Consumer demand for high-quality and personalized health information was exploding as a result of several national trends. The ability to ensure high-quality and personalized search results on the Internet was more critical in the health domain—particularly in the cancer setting—than in any other industry because of the serious consequences associated with the use of unreliable and irrelevant health information.



### Response

NCI funding enabled the development of Healia ([www.healia.com](http://www.healia.com)), a consumer health search engine that addresses the unique complexities of a health information search and provides consumers with reliable and personalized search results. The patent-pending technology of Healia consists of algorithms and methods for evaluating the quality of web content; for categorizing web pages that match specific content types, user preferences, and audience profiles; and for seamlessly integrating search technology with any web application.

### Progress

A comparison of the usefulness of search engines demonstrated the effectiveness of Healia; Healia was rated similarly to Google and significantly better than MedHunt according to several measures. All physicians who participated in the survey rated Healia higher than Google and MedHunt on each dimension of quality.

Users seeking information on cancer prevention and other health issues can search more effectively because of Healia's semantic analyses of search queries that suggest alternative search terms and the

most appropriate resources. Healia is currently the only search engine that can categorize documents by demographic categories such as gender, age, and racial/ethnic background, which enables users to easily filter search results to receive individually relevant results. Although the Healia search engine was officially launched in mid-September 2006, it has already been cited widely by the media and by health and search industry reports.

## RESEARCH DISSEMINATION AND DIFFUSION

### *PROMOTING THE ADOPTION, REACH, AND IMPACT OF EVIDENCE-BASED INTERVENTIONS*

The significant advances noted throughout this report are of limited value unless and until they are translated into evidence-based actions taken by health care practitioners, patient advocates, purchasers and insurers, community-based, employer, and health care organizations, as well as policymakers. The Designing for Dissemination (D4D) (see <http://cancercontrol.cancer.gov/d4d>) team at NCI leads and supports the science of dissemination and implementation, as well as promotes the adoption and adaptation of evidence-based intervention practices, programs, and policies. An important task of the Research Dissemination and Diffusion team is to link the lessons learned from science with the lessons learned from service within NCI (e.g., with the NCI Office of Communication and Education), and to design, implement, and evaluate interagency partnership programs and projects within NIH, the Department of Health and Human Services, and with other government agencies and non-governmental organizations that support research, practice, and policy reducing the burden of cancer. The D4D team also works internationally to promote dissemination and implementation research opportunities to international investigators, as well as to build partnerships to adapt research dissemination tools (for example, see <http://cancercontrolplanet.cancer.gov>) for use by other countries. Thus, the mission of the NCI DCCPS D4D team is to serve as a catalyst to build and sustain the field of dissemination and implementation science in order to enhance the integration of evidence-based guidelines, programs, and policies for cancer control in public health and clinical practice at all levels of health promotion, disease prevention, and health care delivery contexts. The vision of the NCI DCCPS D4D Team is to close the gap between research discovery and program delivery in public health, clinical practice, and health policy across the cancer control continuum from primary prevention to end-of-life care.



# SECTION 7: SPECIAL FEATURES

## SEER: RESEARCH POWER IN NUMBERS



NCI's Surveillance  
Epidemiology and

End Results (SEER) Program is a powerful cancer research tool that has served as the basis for thousands of studies.

Innovative use of SEER data has produced additional statistics such as cancer prevalence, which is important to national estimates of cancer survivorship.

Although many people equate SEER with the *Annual Report to the Nation*, the main reason for its popularity is rooted in the fact that SEER is the most comprehensive, population-based cancer registry in the world. It currently covers 26 percent of the U.S. population, and captures information on patient demographics, primary tumor site and morphology, stage at diagnosis, first course of treatment, and survival.

Since its establishment in 1973, SEER has constantly evolved to become more sophisticated and robust, while still maintaining –and enhancing– data confidentiality. For the past two decades, SEER has worked with the public and private sector, notably the North American Association of Central Cancer Registries, the American Cancer Society, the Commission on Cancer, and the Centers for Disease Control and Prevention to build a more cohesive national cancer registry system. In addition, the establish-

ment of linkages between SEER data and Medicare records have opened up new avenues of cancer research that focus on treatment, particularly quality, patterns, and cost of care.

Quality control is a cornerstone of the SEER Program. In addition to extensive training courses for cancer registry professionals, web-based tools are used for distance learning and to conduct reliability studies, the results of which are used to target future training and improve data quality. SEER also is applying contemporary information technology enhancements to improve efficiency, including a modular data management system and sophisticated tools for identifying cancer cases based on electronic capture of information in pathology records.

In addition, since the 1990s, SEER has worked with the intramural and extramural research teams to conduct Rapid Response Surveillance Studies –investigations that can be performed in a relatively short period of time, typically one to two years. Numerous papers have been published based on these studies that address important questions about the dissemination of treatment advances in the community and other cancer control efforts that, in the absence of SEER, would take far longer to answer.

And, of course, a unique aspect of SEER that has made it a tremendous gateway for public health information is its limited use file, available for analysis to users who agree to maintain confidentiality



protections. The SEER Program has been at the forefront of providing access to cancer data for both public health professionals and the advocacy community through user-friendly analytical tools.

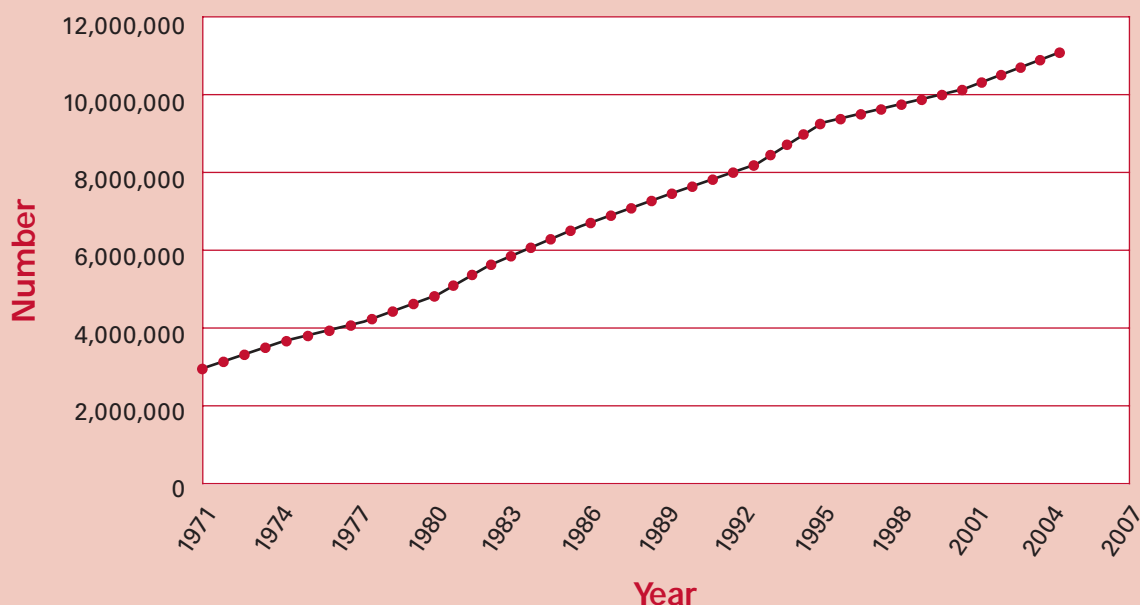
These are just a taste of the scope of the SEER Program and the vital research it supports. SEER continues to be an important resource for the public health community, using population-based science to have a significant impact on measuring our nation's progress in cancer prevention and treatment and guiding future directions for cancer research.

*Reprinted from NCI Cancer Bulletin*

*SEER is a mainstay of the National Cancer Program. It is the backbone for studies of environmental influences on cancer, for examination of cancer survival among our population, and for measuring our progress against cancer for the Nation as a whole. Rational leadership of NCI would not be possible without SEER.*

*Peter Greenwald, M.D., Dr.P.H.  
Director,  
Division of Cancer Prevention, NCI*

**Cancer Prevalence Graph:** Estimated Number of Cancer Survivors in the United States from 1971 to 2005



Data source: Surveillance, Epidemiology, and End Results (SEER) Program ([www.seer.cancer.gov](http://www.seer.cancer.gov)). Prevalence database: "US Estimated 30-Year L-D Prevalence Counts on 1/1/2005 by Duration." National Cancer Institute, DCCPS, Surveillance Research Program, Statistical Research and Applications Branch, released April 2008, based on the November 2007 SEER data submission.

## ACKNOWLEDGING OUR RESEARCH COMMUNITY

In order to truly celebrate the division's 10-year anniversary milestone, DCCPS must recognize the awards and contributions of our grantees. The division currently funds more than 900 grants valued at almost \$400 million. In addition, investigators are funded through research contracts, with the largest investment made in our multiple SEER registries across the United States. The researchers funded by DCCPS have advanced the science to improve public health over the past 10 years, and we celebrate their contribution.

We have developed several web tools to highlight our investigators and the research they are conducting.

### CC CITATIONS

<http://citations.cancer.gov>

CC Citations is a searchable database that includes information on publications by staff, grantees, and contract-funded investigators. This database demonstrates the depth and breadth of research publica-

tions resulting from studies funded by DCCPS. CC Citations currently includes DCCPS staff and grantee publications from 2005-2006. It not only highlights our grantee and staff research publications but also communicates the return on investment to our stakeholders and constituents.

### RESEARCH PORTFOLIO

[www.cancercontrol.cancer.gov/grants/query.asp](http://www.cancercontrol.cancer.gov/grants/query.asp)

Research Portfolio provides a list of grants funded in DCCPS. The information on each grant includes the name of the principal investigator and of the organization, the title of the grant and the abstract, the grant number, and a link to publications in PubMed that cite the grant number.

### MAPS WEB SITE

<http://maps.cancer.gov/overview/map/index.jsp>

DCCPS supports research projects at institutions within the United States and internationally. The U.S. Maps web site provides tables and maps illustrating the number of grants and dollars awarded by state (including the District of Columbia), territory, county, congressional district, and institution.

The majority of DCCPS-supported research projects are in the United States; however, we also have an international site that provides information on the foreign piece of our portfolio. This map represents the country in which the



<http://cancercontrol.cancer.gov>

primary grant award was made and does not reflect performing sites within each grant. Maps can be viewed either by the number of grants or by awarded dollars.

#### 10-YEAR WEB SITE

[http://cancercontrol.cancer.gov/10years/10\\_years.asp](http://cancercontrol.cancer.gov/10years/10_years.asp)

The 10-Year web site includes four web pages highlighting the accomplishments of our grantee community. The Pioneers in Cancer Control Research page includes researchers who were funded when DCCPS was formed in 1997 and still hold grants in our division today. These pioneers have helped to enhance and

expand cancer control and population science research over the past decade. The MERIT Awardees page highlights the DCCPS grantees who have received the Method to Extend Research in Time (MERIT) Award, given by the NIH to recognize superior researchers. The Star RO1 Investigators page lists all of the new investigators in DCCPS since 1999 (when this information was first tracked). The BSA/NCAB Members page lists the DCCPS grantees who have served on the Board of Scientific Advisors (BSA) or the National Cancer Advisory Board (NCAB) between 1997 and 2007.

We applaud the work of our research community and look forward to the next 10 years of advancing the science to improve public health.





## ADVANCING THE SCIENCE OF TEAM SCIENCE

A key strategy for achieving the goals of DCCPS is the development of new transdisciplinary team science research centers, focused on domains that are seen as critical barriers against effective cancer prevention and control. It was clear from the outset that to effectively accomplish the program objectives, both the centers' projects and investigators would need to span a wide range of disciplines, from molecular biology to policy studies.

Two critical issues emerging from these efforts concern the relative merits of these investments versus traditional discipline-specific activities, and how best to ensure their success. Funders and investigators alike are asking, 'How do we evaluate transdisciplinary team science?'

Once these centers were launched, it immediately became evident that the NIH, including NCI, had no clear metrics for evaluating problem-focused initiatives such as the Transdisciplinary Tobacco Use Research Centers (TTURCs). In addition, the specific goals of the TTURCs were based on assumptions about how best to facilitate scientific progress that had yet to be tested empirically. Thus, the centers' initiatives presented a challenge to the science of evaluation as well as an opportunity to develop new evaluation methods by studying the processes and outcomes of transdisciplinary science itself.

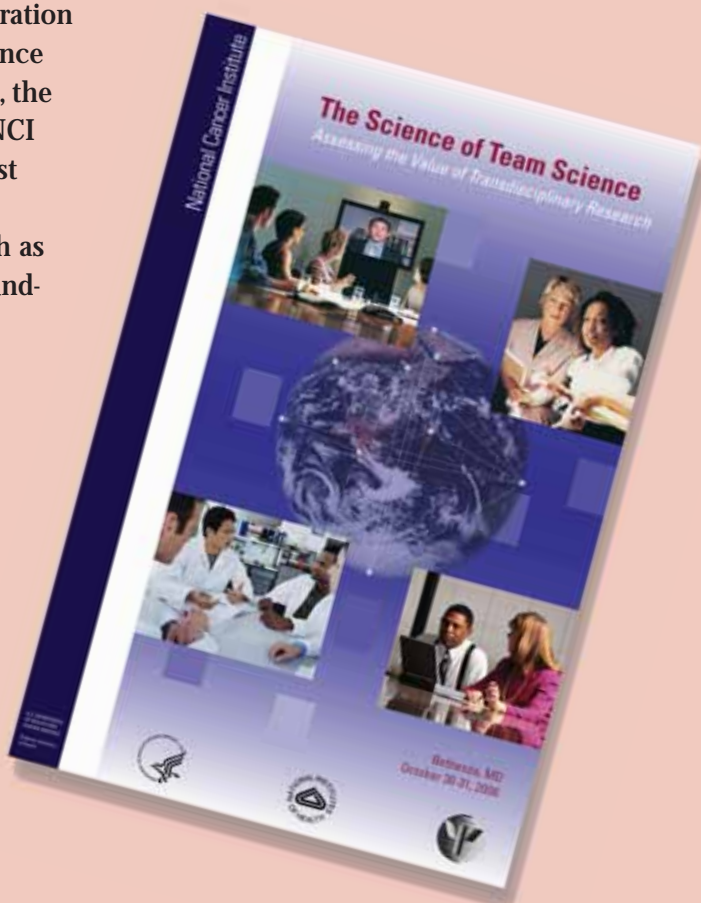
As such, an evaluation methods development effort was initiated in order to focus on the assessment of constructs, such as collaboration and transdisciplinarity, that were deemed essential to the process of planning and conducting transdisciplinary science. The Evaluation of Large Initiatives (ELI) Project was launched in 2000 as an effort to specify, measure, and understand the transdisciplinary science goals and processes within the TTURCs. William Trochim, PhD, Cornell University, was asked to lead this initial effort.

Under Dr. Trochim's leadership, the ELI team developed a set of metrics and methods that could be applied to evaluating the TTURCs, some of which have been subsequently utilized in evaluating large initiatives at other centers, including Centers for Population Health and Health Disparities (CPHHD), Centers of Excellence in Cancer Communication Research (CECCR), and Transdisciplinary Research in Energetics and Cancer (TREC) centers. From these efforts, it became evident that an expanded effort focusing on the "science of team science" was merited.

Dan Stokols, PhD, University of California – Irvine, was asked to lead this second phase of the ELI Project, which included the evaluation of the TREC centers and the planning of the Science of Team Science conference, which formed the basis of a special supplement of the *American Journal of Preventive Medicine* (AJPM), published in 2008. Organized by the ELI team, this conference was held in

October 2006, and brought in leaders from many areas to disseminate their transdisciplinary-related research and stimulate discussion regarding the next steps in studying the science of team science.

Other activities of the ELI Project have included, in collaboration with NCI's Office of Science Planning and Assessment, the development of a Trans-NCI Evaluation Special Interest Group to discuss issues related to evaluation such as measures, metrics, and funding mechanisms. As the science of team science progresses, the ELI team continues to develop new ways of studying this important area and serves as a resource for all of DCCPS.



## EXAMPLES OF CURRENT MAJOR INITIATIVES

Below are some selected examples of major initiatives currently funded by the division. For a complete listing of DCCPS major initiatives, please visit <http://initiatives.cancer.gov/archive/>

### TRANSDISCIPLINARY TEAM SCIENCE CENTERS



### EPIDEMIOLOGY CONSORTIA & HIGH CANCER RISK REGISTRIES



### SURVIVAL & OUTCOMES NETWORKS



### INTEGRATED NATIONAL CANCER CONTROL SURVEILLANCE SYSTEM



### HEALTH SURVEYS SUPPORTED AND CO-FUNDED BY DCCPS





Thank you to our partners on these initiatives.  
Please also see our full listing of collaborators and partners on page 14.

#### PARTICIPATING PARTNERS:

National Institute for Environmental Health Sciences  
National Institute of Environmental Health Sciences  
National Institute on Aging  
National Institute on Alcohol Abuse and Alcoholism  
National Institute on Drug Abuse  
Office of Behavioral and Social Sciences Research  
Robert Wood Johnson Foundation

#### PARTICIPATING PARTNER:

Division of Cancer Epidemiology and Genetics, NCI

#### PARTICIPATING PARTNERS:

Agency for Healthcare Research and Quality  
American Cancer Society  
Cancer Information Service, NCI  
Department of Veterans Affairs

#### PARTICIPATING PARTNERS:

American Cancer Society  
Centers for Disease Control and Prevention  
Centers for Medicare and Medicaid Services  
Commission on Cancer of the American College of Surgeons  
National Center for Health Statistics, CDC  
National Heart Lung and Blood Institute  
National Institute on Aging  
National Program of Cancer Registries, CDC  
North American Association of Central Cancer Registries  
U.S. Census Bureau

#### PARTICIPATING PARTNERS:

Abt Associates, Inc.  
California Department of Health Services  
National Center for Health Statistics, CDC  
Public Health Institute  
UCLA Center for Health Policy Research  
U.S. Census Bureau





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