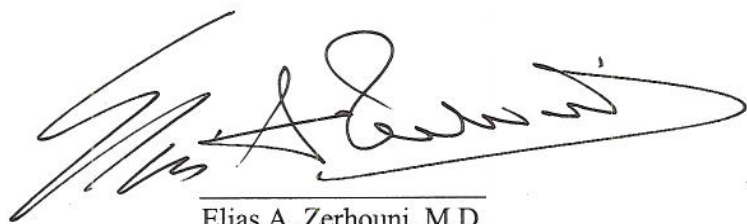


DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

**NCI 2005 Progress Report on the NIH Prostate Cancer Research Plan
FY 2003 – FY 2008**

A handwritten signature in black ink, appearing to read 'Elias A. Zerhouni', written over a horizontal line.

Elias A. Zerhouni, M.D.
Director, NIH

February 2006

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**NCI 2005 Progress Report on the NIH Prostate Cancer Research Plan
FY 2003 – FY 2008**

Executive Summary

In House report No. 109-143, the Committee on Appropriations requested that the National Cancer Institute (NCI) provide an annual update on its progress in prostate cancer research with respect to the goals outlined in the *NIH Prostate Cancer Research Plan FY 2003 – FY 2008*. The following is submitted in response to that request.

Biology, Progression, and Metastasis: NCI-sponsored researchers recently identified genes that appear to be associated with increased risk of developing prostate cancer, as well as factors that control metastasis. NCI initiated or continued several initiatives designed to improve research methods and technology relevant to the biology, progression, or spread of prostate cancer.

Etiology and Prevention: NCI-sponsored studies have identified dietary factors and physical characteristics that are associated with higher and lower risk of developing prostate cancer. NCI continues its support of programs that will lead to the identification of risk factors and the clinical evaluation of preventive measures for cancer.

Early Detection, Diagnosis, and Prognosis: NCI-sponsored researchers have recently assessed the value of prostate-specific antigen (PSA) testing in different populations and have compared outcomes in men with higher and lower PSA velocities (rate of change in PSA levels). NCI continues to support initiatives related to prostate cancer early detection, diagnosis, and prognosis.

Treatment: NCI-sponsored research projects and clinical trials have led to new treatments for prostate cancer. NCI continues to support initiatives that fund research on the development and validation of optimal treatments for prostate cancer, ranging from evaluating the biologic effects of agents undergoing clinical trial to accelerating the transfer of new treatment strategies from the laboratory to the clinic.

Cancer Control, Survivorship, and Outcomes: NCI-supported researchers have recently examined the impact of prostate cancer treatment on the risk of developing rectal cancer and bone fractures, as well the effectiveness of observation and delayed androgen withdrawal. NCI continues to support research on prostate cancer patient survivorship, end-of-life care, treatment outcomes, and behaviors.

Laboratory and Preclinical Models: Several new mouse models of human prostate cancer have been developed through NCI support that more accurately represent human disease and have improved the understanding of biologic effects of certain treatments.

Resource and Capacity Building: NCI renewed or launched many initiatives, including the Cancer Biomedical Informatics Grid (caBIG) and the Health Information National Trends Survey (HINTS) website, that will provide tools and support researchers need in order to make progress against prostate cancer.

NCI 2005 Progress Report on the NIH Prostate Cancer Research Plan FY 2003 – FY 2008

Introduction

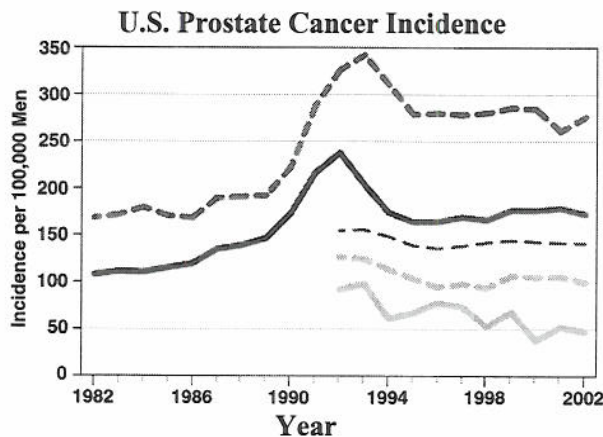
In its report on the Fiscal Year (FY) 2006 budget for the Department of Health and Human Services, the Committee on Appropriations stated the following:

The Committee recognizes NCI's commitment to prostate cancer research as laid forth in its "Prostate Cancer Research Plan, FY 2003—FY 2008." The Committee requests that NCI provide an annual update every January on its progress in prostate cancer research as it reflects the goals outlined in the plan for years fiscal years 2006–08. In developing this update the Committee urges the NIH to consult and work closely with the research community, clinicians, and patient advocacy groups and the Congress. (House report No.109-143, page 57)

The following report has been prepared by the National Cancer Institute (NCI) within National Institutes of Health of the Department of Health and Human Services in response to this request.

Prostate Cancer Disease and Funding Trends

Data from NCI's Surveillance, Epidemiology, and End Results (SEER) program show that over the last 30 years, the 5-year survival rate for prostate cancer patients has risen from 67% in 1974-1976 to 75% for 1983-1985, to 99% for 1995-2000.¹ For U.S. men, prostate cancer is the most common cancer, excluding skin cancer, and the second-most common cause of cancer-related deaths. Over the last two decades, African American men have had higher incidence and mortality rates than men of other racial and ethnic groups (see Figures 1 and 2).



¹ Jemal, et al. Cancer Statistics, CA Cancer J Clin. 2005 Jan-Feb;55(1):10-30, table 11.

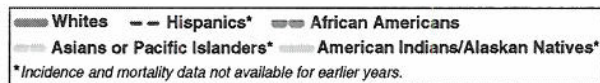
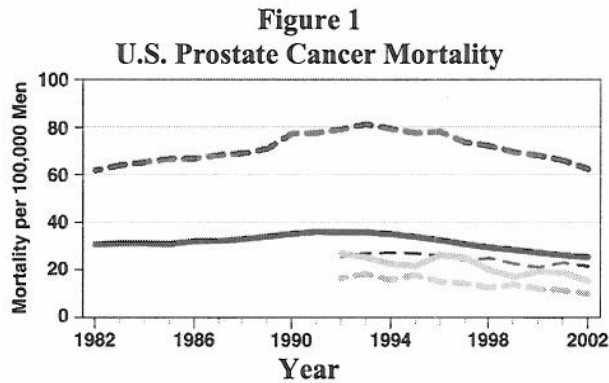
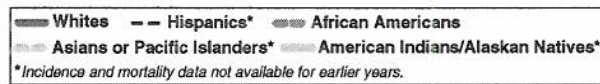


Figure 2

Prostate cancer incidence rates rose dramatically in the late 1980s. This increase corresponds to improvements in detection and diagnosis through widespread use of prostate-specific antigen (PSA) testing, which received initial U.S. Food and Drug Administration approval in 1986. In the early 1990s, prostate cancer incidence began declining and then leveled off in recent years. Prostate cancer death rates have declined since the early 1990s. It is estimated that around \$8.0 billion² is spent on prostate cancer treatment each year in the United States.

² In 2004 dollars, using methods described in: Brown ML, Riley GF, Schussler N, Etzioni RD. Estimating health care costs related to cancer treatment from SEER-Medicare data. *Medical Care* 2002 Aug;40(8 Suppl):IV-104-17.

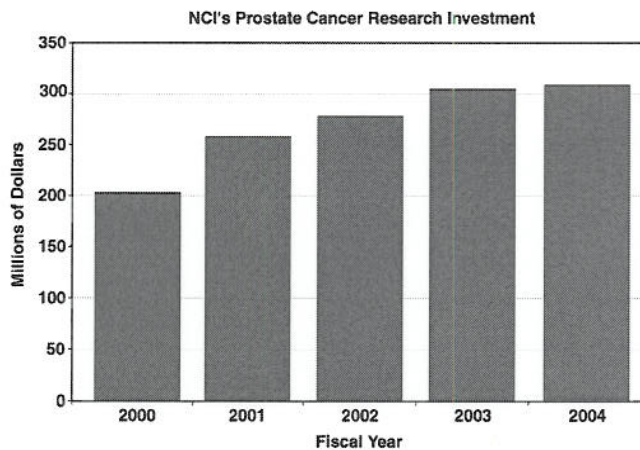


Figure 3

NCI increased its overall support for prostate cancer research from \$203.2 million in FY 2000 to \$308.5M in FY 2004 (see Figure 3). This 52% increase in support for prostate cancer is greater than the increase in the overall NCI budget (43%) during these years.

Prostate Cancer Research Plan for FY 2003 – FY 2008

In 2001, the Senate Committee on Appropriations (report no. 107-84, page 125) requested the NIH prepare and submit a prostate cancer research plan to address concerns that “prostate cancer research has not kept pace with scientific opportunities and the proportion of the male population afflicted with the disease.”

The development of the NIH plan included consultation with cancer researchers, clinicians, and advocacy groups. As the lead institute for cancer research at NIH, NCI prepared a prostate cancer research plan that serves as the core of the NIH Prostate Cancer Research Plan FY 2003 – FY 2008. Research plans and activities of seven other NIH institutes and centers with significant prostate cancer research portfolios were also included.

The NCI component of the NIH plan outlined goals, objectives, and near-term milestones in seven different scientific areas that span the continuum of research: (1) Biology, Progression, and Metastasis; (2) Etiology and Prevention; (3) Early Detection, Diagnosis, and Prognosis; (4) Treatment; (5) Cancer Control, Survivorship, and Outcomes; (6) Laboratory and Preclinical Models; and (7) Resources and Capacity Building.

Progress in Achieving the Goals of the Prostate Cancer Research Plan

NCI has prepared the following report to describe progress made by NCI in 2005 in achieving the goals and objectives laid out in the *NIH Prostate Cancer Research Plan*. The new report has seven sections corresponding to the seven scientific areas of the Plan. Each section includes selected examples of relevant NCI research results and initiatives, as well as clinical trials when applicable.

Biology, Progression, and Metastasis

Goal: Elucidate the molecular and cellular processes that lead to prostate cancer initiation, progression, and metastasis.

Recent Results from NCI-Sponsored Research

- In a study of 400 men with prostate cancer, researchers showed that low levels of the protein Alpha-Methylacyl-CoA Racemase (AMACR) in prostate cancer tissue may be an important biomarker for aggressive prostate cancer. A study to confirm these results in 1,300 patients is currently underway.³
- A recent study showed that the tumor suppressor gene Deleted in Liver Cancer-1 (DLC-1) is often silenced in both prostate cancer and benign prostatic hyperplasia. This finding may ultimately be useful for the early detection of prostate cancer.
- Since prostate cancer that has spread beyond the prostate gland cannot be cured, it is important to identify factors implicated in the spread of tumor to nearby lymph nodes and distant sites. Researchers recently demonstrated that little or no Ephrin B4 (EphB4) protein activity occurred in benign prostate epithelial cells, but EphB4 was expressed in all prostate cancer cell lines studied. EphB4 therefore shows promise for diagnostic, prognostic, and therapeutic research.⁴
- Certain mutations in the androgen receptor (AR) protein cause advanced and invasive prostate cancer when put into otherwise healthy mice. Because similarly defective ARs have been found in patients with prostate cancer whose disease is androgen independent, the finding helps explain why most men with advanced prostate cancer treated with hormone-withdrawal therapy are not cured.⁵

New and Continued Prostate-Relevant Initiatives

- Activities to Promote Research Collaborations encourages scientific collaboration among NCI grantees, as well as with other members of the scientific community.

Recently, NCI continued the Innovative Technologies for the Molecular Analysis of Cancer Technologies Program with three specific initiatives:

- Application of Emerging Technologies for Cancer Research evaluates the usefulness of new technologies in appropriate biological contexts to assess their

³ Published in Rubin MA, et al. Decreased alpha-methylacyl CoA racemase expression in localized prostate cancer is associated with an increased rate of biochemical recurrence and cancer-specific death. *Cancer Epidemiol Biomarkers Prev.* 2005 Jun;14(6):1424-32.

⁴ Published in Xia G., et al. EphB4 expression and biological significance in prostate cancer. *Cancer Res.* 2005 Jun 1;65(11):4623-32.

⁵ Published in Han G, et al. Mutation of the androgen receptor causes oncogenic transformation of the prostate. *Proc Natl Acad Sci U S A.* 2005 Jan 25;102(4):1151-6. Epub 2005 Jan 18.

reproducibility and produce preliminary data toward a biological or clinical question.

- Innovative Technologies for the Molecular Analysis of Cancer supports research on developing innovative cancer-relevant molecular technologies.
- Innovations in Cancer Sample Preparation funds projects designed to optimize the usefulness of biological samples.

Etiology and Prevention

Goal: Discover genetic, biochemical, environmental, and lifestyle factors and their interactions that define prostate cancer risk, play causal roles in its initiation and progression, and inform the development of new strategies for prevention and early detection.

Recent Results from NCI-Sponsored Research

- Obesity may increase the risk of aggressive forms of prostate cancer, possibly because excess fat suppresses PSA levels in the blood. This study of 787 men undergoing biopsy after receiving a high PSA test result also showed that a high body-mass index (BMI) was associated with a higher risk of being diagnosed with prostate cancer.
- A case-control analysis of 300 men found that those with higher levels of vitamin E had a lower risk of developing prostate cancer. Men with the highest levels of alpha-tocopherol, a form of vitamin E, had a 53% lower risk, while those with high levels of gamma-tocopherol, another form of vitamin E, had a 39% reduction in risk.⁶
- A study of 34,428 men found that those who used cholesterol-lowering drugs, such as statins, had significantly less risk of advanced prostate cancer and metastatic or fatal prostate cancer than nonusers of these drugs.

New and Continued Prostate-Relevant Initiatives

The following NCI initiatives were new in 2005 and address some of the objectives in the *NIH Prostate Cancer Research Plan FY 2003 – FY 2008*. Future awards for prostate cancer research under these initiatives are contingent on the receipt of applications for prostate-related projects and peer review evaluation of these applications.

- The Gene Expression Database of Normal Human Organ Tissue is the largest open-source database for normal tissue from human organs, and can be used to identify genes that cause disease.
- Stem Cells and Cancer stimulates research on all aspects of stem cell biology, including research into the molecular and biochemical regulation of embryonic and adult stem cell behavior, to identify the cells responsible for disease progression and metastasis.

⁶ Published in Weinstein SJ, et al. Serum alpha-tocopherol and gamma-tocopherol in relation to prostate cancer risk in a prospective study. *J Natl Cancer Inst.* 2005 Mar 2;97(5):396-9.

- The Breast and Prostate Cancer and Hormone-Related Gene Variants Cohort Consortium pools data and biospecimens from six large cohorts to conduct research on gene-environment interactions in cancer etiology.
- The Cancer Genetic Markers of Susceptibility (C-GEMS) project uses cutting-edge technology to help identify inherited susceptibility genes for breast and prostate cancer.

In 2005, NCI continued the following initiative, which supports research on prostate cancer:

- The Small Grants Program for Cancer Epidemiology supports epidemiology studies focusing on cancer etiology.

Clinical Trials

NCI prevention clinical trials initiated or active in 2005 include the following:

- The Selenium and Vitamin E Cancer Prevention Trial (SELECT)—Evaluating the protective benefits of selenium and vitamin E on the incidence rate of prostate cancer.
- Phase III Randomized Study of Selenium as Chemoprevention of Prostate Cancer in Patients with High-Grade Prostatic Intraepithelial Neoplasia—Evaluating the effects of selenium on the incidence rate of prostate cancer in patients with high-grade prostatic intraepithelial neoplasia.
- Phase II Randomized Study of Dietary Soy in Patients with Elevated Prostate-Specific Antigen (PSA) Levels—Determining the effectiveness of soy protein supplements in preventing prostate cancer in patients with high PSA levels.
- Phase II Study of Pomegranate Juice in Patients with Indication of Recurrent Adenocarcinoma of the Prostate—Determining whether pomegranate juice can decrease or slow rising PSA levels in patients who have undergone treatment for prostate cancer.
- Identification of Genes Associated with Cancer in Patients and Siblings Who Have Cancer—Assessing whether certain genes are associated with cancer in patients with cancer of the breast, prostate, lung, or colon and siblings of these patients.

Early Detection, Diagnosis, and Prognosis

Goal: Use knowledge gained about the molecular and cellular biology of prostate cancer to develop improved methods for detecting and diagnosing pre-malignant and malignant lesions and for better predicting disease progression and response to therapy.

Recent Results from NCI-Sponsored Research

- Men with higher rates of change in PSA values (PSA velocity) in the year before treatment for localized prostate cancer are more likely to have their prostate cancer recur and are likely to die sooner than men with lower PSA velocities.⁷
- Early data from the prostate cancer screening arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial show that men with a PSA test result of 7 ng/ml or greater are more likely to have a subsequent prostate biopsy than men with lower but still abnormal test results. Men with a positive digital rectal exam without a positive PSA test were less likely to receive a biopsy than men with a positive PSA test.⁸
- Researchers analyzed data from 8,575 healthy men to determine the relative sensitivity (percentage of true positive results) and specificity (percentage of true negative results) of PSA screening. They found that sensitivities and specificities varied widely, and concluded that a man's risk of developing prostate cancer cannot be determined solely from his PSA level.⁹
- Researchers recently created a reliable method to calibrate instruments in different laboratories to detect potential cancer biomarker proteins with the same accuracy. The method uses surface-enhanced laser desorption (SELDI) mass spectrometry (MS) to help clinicians detect protein biomarkers for prostate cancer. NCI is now testing whether the technique correctly classifies prostate cancers and controls from different institutions.¹⁰
- A study of 2,779 men without prostate cancer showed that about one-third of those who were obese and overweight had lower levels of PSA, which may help explain why obesity appears to increase the risk of aggressive forms of prostate cancer. Because of this, PSA screening in overweight and obese men could produce false-negative results and delay the diagnosis of prostate cancer.¹¹

New and Continued Prostate-Relevant Initiatives

- Correlative Studies with Specimens from Multi-Site Trials initiative fosters collaborations and interactions between basic researchers, scientists working in

⁷ Published in D'Amico AV, et al. Pretreatment PSA velocity and risk of death from prostate cancer following external beam radiation therapy. *JAMA*. 2005 Jul 27;294(4):440-7.

⁸ Published in Pinsky PF, et al. Prostate biopsy following a positive screen in the prostate, lung, colorectal and ovarian cancer screening trial. *J Urol*. 2005 Mar;173(3):746-50; discussion 750-1.

⁹ Published in Thompson IM, et al. Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/ml or lower. *JAMA*. 2005 Jul 6;294(1):66-70.

¹⁰ Published in Semmes OJ, Feng Z, et al. Evaluation of serum protein profiling by surface-enhanced laser desorption/ionization time-of-flight mass spectrometry for the detection of prostate cancer: I. Assessment of platform reproducibility. *Clin Chem*. 2005 Jan;51(1):102-12.

¹¹ Published in Baillargeon J, et al. The association of body mass index and prostate-specific antigen in a population-based study. *Cancer*. 2005 Mar 1;103(5):1092-5.

private industry, and clinical investigators to perform clinical translational research on promising predictive and prognostic markers.

- A task force is planning the Prostate Specialized Program of Research Excellence (SPORE) National Biospecimen Network Pilot. This pilot project will provide an ongoing platform for the prostate cancer SPOREs to test and validate prostate cancer biomarkers.
- Prostate cancer diagnosis is the target for one of the recently awarded NCI Centers of Nanotechnology Excellence. The focus for the development of this novel platform will be a nanofluidics platform capable of measuring a large number of genetic changes in prostate cancer.

Clinical Trials

NCI clinical trials related to early detection, diagnosis, and prognosis initiated or active in 2005 include the following:

- Phase I/II Pilot Study of Computed Tomography (CT) Scans Using CT-On-Rails™ For Localization in the Treatment of Patients with Prostate Cancer—Evaluating how well CT scans using CT-on-rails™ work in pinpointing the location of tumors in patients with prostate cancer.
- Diagnostic Study of Positron Emission Tomography Using Carbon-11 Acetate in Detecting Metastasis and Predicting Recurrence in Patients with Newly Diagnosed Prostate Cancer at Medium or High Risk for Recurrence after Initial Curative Therapy—Studying the effectiveness of positron emission tomography using carbon-11 acetate in finding metastasis and predicting recurrence in patients with prostate cancer who are at risk for recurrence after treatment.
- Diagnostic Pilot Study of Magnetic Resonance Imaging of Lymph Nodes Using Ferumoxytol in Patients with Primary Prostate or Breast Cancer— Studying how well magnetic resonance imaging (MRI) using ferumoxytol works in detecting metastases to the lymph nodes in patients with primary prostate or breast cancer.
- Diagnostic Study of Dynamic Contrast-Enhanced MRI Using the Access to Prostate Tissue Under MRI Guidance System (APT-MRI) for Prostate Cancer Delineation and Characterization in Patients with Confirmed or Suspected Adenocarcinoma of the Prostate—Assessing the effectiveness of MRI in finding cancer and determining the extent of disease in patients with confirmed or suspected prostate cancer.

Treatment

Goal: Accelerate development and validation of optimal treatments that target the molecular and cellular characteristics of prostate cancer.

Recent Results from NCI-Sponsored Research

- In a recent clinical trial, 770 men with advanced prostate cancer who were no longer responding to hormonal therapy were randomly assigned to receive prednisone and mitoxantrone, the only currently approved treatment for these

patients, or docetaxel and estramustine. Those who took docetaxel and estramustine lived a median of 18 months—two months longer than men taking prednisone and mitoxantrone.¹²

- Ten radiation treatment sessions over 2 weeks significantly reduces pain in 50-80% of prostate cancer patients with painful bone metastases. However, a recent study showed that a single dose appears to alleviate bone pain just as well and with fewer side effects.¹³
- When 695 men in Sweden, Finland, and Iceland (where prostate cancer is typically diagnosed at later stages than in the United States) with early-stage prostate cancer were followed for 8.2 years, 30 men who received surgery died from prostate cancer compared to 50 in the watchful waiting group—a 44% advantage. Moreover, men who underwent surgery were 26% less likely to die of all causes than those in the watchful waiting group.¹⁴
- A pilot study has found that a cancer vaccine can be safely given to patients undergoing radiation therapy. Some patients who received the vaccine developed an immune response against tumor cells, indicating that their bodies were fighting the cancer.¹⁵

New and Continued Prostate-Relevant Initiatives

- The Quick-Trials for Novel Cancer Therapies: Exploratory Grants Program significantly reduces the turnaround time from application submission to funding for pilot, Phase I, and Phase II cancer clinical trials, and for patient monitoring and laboratory studies linked to cancer clinical trials.
- Rapid Access to Intervention Development (RAID) offers investigators access to the drug development contract resources of NCI's Developmental Therapeutics Program to accelerate the translation of novel molecules and concepts to the clinic for clinical trials.
- Early Therapeutics Development with Phase II Emphasis evaluates biologic effects of NCI-sponsored agents in Phase II and early clinical trials on their molecular targets, evaluates other relevant biologic effects, and determines clinically relevant outcomes/correlates.

¹² Published in Petrylak DP, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med.* 2004 Oct 7;351(15):1513-20.

¹³ Published in William F. Hartsell, et al. Randomized Trial of Short- Versus Long-Course Radiotherapy for Palliation of Painful Bone Metastases. *J Natl Cancer Inst* 2005; 97: 798-804.

¹⁴ Published in Bill-Axelsson A, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med.* 2005 May 12;352(19):1977-84.

¹⁵ Published in Gulley JL, et al. Combining a recombinant cancer vaccine with standard definitive radiotherapy in patients with localized prostate cancer. *Clin Cancer Res.* 2005 May 1;11(9):3353-62.

Clinical Trials

The following are a sampling of treatment-related NCI clinical trials that began or were active in 2005:

- Phase III Randomized Study of Total Androgen Blockade with or without Pelvic Irradiation in Patients with Locally Advanced Adenocarcinoma of the Prostate—Comparing hormone therapy alone to combined hormone therapy and bilateral orchiectomy or radiation therapy in patients with stage III or stage IV prostate cancer.
- Phase III Randomized Study of High- Versus Standard-Dose Three-Dimensional Conformal or Intensity-Modulated Radiotherapy in Patients with Stage I or II Adenocarcinoma of the Prostate—Comparing the effectiveness of two different doses of specialized radiation therapy in treating patients who have stage I or stage II prostate cancer.
- Phase II Randomized Study of Neoadjuvant CCI-779 Followed by Radical Prostatectomy in Patients with Newly Diagnosed Prostate Cancer Who Have a High Risk of Relapse—Assessing the effectiveness of CCI-779 in treating patients who are undergoing radical prostatectomy for newly diagnosed prostate cancer at high risk of relapse.
- Phase I Study of Ketoconazole and Docetaxel in Patients with Metastatic Androgen-Independent Prostate Cancer—Studying the effectiveness of combining ketoconazole with docetaxel in treating patients who have metastatic prostate cancer.

Cancer Control, Survivorship, and Outcomes

Goal: Achieve a continuously improved understanding of the impact of prostate cancer and its care on individuals, families, and populations with special emphasis on enhancing survivorship, improving quality of care, and steadily reducing disparities in both care and outcomes.

Recent Results from NCI-Sponsored Research

- Men are significantly less likely to continue prostate cancer screening after they receive a false-positive prostate cancer screening result. In addition, African Americans and men with less than a high school education are less likely to seek screening than other men.¹⁶
- Although the risk of developing rectal cancer after radiation treatment for prostate cancer is low, men treated who have received external radiation with or without surgery have nearly twice the risk of rectal cancer of those whose

¹⁶ Published in Ford ME, et al. Effects of false-positive prostate cancer screening results on subsequent prostate cancer screening behavior. *Cancer Epidemiol Biomarkers Prev.* 2005 Jan;14(1):190-4.

prostate cancer was treated with surgery alone. More targeted treatment, such as conformal radiation, may reduce risk to the rectum.¹⁷

- Androgen deprivation therapy, which is becoming increasingly popular, is associated with an increased risk of bone fracture in elderly men with prostate cancer.¹⁸
- A risk analysis of 767 men in the Connecticut Tumor Registry diagnosed with localized prostate cancer between 1971 and 1984 treated by observation or delayed androgen withdrawal found that the death rate in these patients has remained stable and low after more than 20 years of follow-up.¹⁹

New and Continued Prostate-Relevant Initiatives

The following NCI initiatives were new in 2005 and address some of the objectives in the *NIH Prostate Cancer Research Plan FY 2003 – FY 2008*. Future awards for prostate cancer research under these initiatives are contingent on the receipt of applications for prostate-related projects and peer review evaluation of these applications.

- Research on the Economics of Diet, Activity, and Energy Balance supports consumer economics, industrial organization, community structure, policy, and cost-effectiveness/cost benefit studies.
- Decision Making in Health: Behavior Maintenance addresses basic decision-making processes underlying initiation and long-term maintenance of healthy lifestyle behaviors that may reduce a person's risk of cancer.

In 2005, NCI continued the following initiative, which supports research on prostate cancer:

- Comprehensive Minority Institution/Cancer Center Partnership is designed to elucidate the reasons for the significant cancer disparities in minority populations.

Clinical Trials

NCI clinical trials related to cancer control, survivorship, and outcomes that began or were active in 2005 include the following:

- Phase III Randomized Study of Gabapentin for the Management of Hot Flashes in Patients with Prostate Cancer—Determining the effectiveness of gabapentin in managing hot flashes in men with prostate cancer.

¹⁷ Published in Baxter NN, et al. Increased risk of rectal cancer after prostate radiation: a population-based study. *Gastroenterology*. 2005 Apr;128(4):819-24.

¹⁸ Published in Shahinian VB, et al. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med*. 2005 Jan 13;352(2):154-64.

¹⁹ Published in Albertsen et al. 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA*. 2005 May 4;293(17):2095-101.

- Phase III Randomized Study of Octreotide for Prevention of Acute Diarrhea in Patients Receiving Radiotherapy to the Pelvis—Determining the effectiveness of octreotide in reducing acute treatment-related diarrhea in patients receiving external-beam radiotherapy to the pelvis.
- Phase II Randomized Study of Erectile Dysfunction Rehabilitation and Unilateral Cavernous Nerve-Sparing Radical Prostatectomy with Versus without Unilateral Autologous Interposition Sural Nerve Grafting in Patients with Clinically Localized Prostate Cancer—Comparing combined nerve grafting and standard therapy with standard therapy alone in treating erectile dysfunction in patients undergoing nerve-sparing radical prostatectomy for localized prostate cancer.
- Phase II Study of APC8015F in Patients with Progressive Metastatic Prostate Cancer and Disease-Related Pain—Assessing the safety of APC8015F in patients with metastatic prostate cancer who had objective disease progression and disease-related pain.

Laboratory and Preclinical Models

Goal: Develop and validate accurate prostate cancer models and ensure that they are integrated into research on the biology, prevention, early detection, and treatment of prostate cancer.

Recent Results from NCI-Sponsored Research

- A new mouse model, knock-in mouse adenocarcinoma prostate (KIMAP), produces heterogeneous and multifocal tumors similar to human prostate cancer. Several tumor marker genes characteristic of human prostate cancer were identified in KIMAP tumors.²⁰
- Researchers have created an in vivo rodent model of prostate cancer development using transplants of tissue that combine rat cells with retroviral-infected human prostate epithelial cell cultures. This model shows that the c-MYC gene is sufficient to induce the development of cancer.²¹
- A new mouse model was produced that develops spontaneous prostate cancer. The resulting mice were used to show that androgen removal allows certain prostate cells to respond after vaccination.²²
- Androgen ablation diminishes tumor formation by suppressing vascular endothelial growth factor (VEGF) production, while androgen-independent disease is marked by androgen-independent VEGF production. An androgen-

²⁰ Published in Gabriel MY, et al. A novel knock-in prostate cancer model demonstrates biology similar to that of human prostate cancer and suitable for preclinical studies. *Mol Ther.* 2005 Mar;11(3):348-62.

²¹ Published in Williams K, et al. Unopposed c-MYC expression in benign prostatic epithelium causes a cancer phenotype. *Prostate.* 2005 Jun 1;63(4):369-84.

²² Published in Drake CG, et al. Androgen ablation mitigates tolerance to a prostate/prostate cancer-restricted antigen. *Cancer Cell.* 2005 Mar;7(3):239-49.

sensitive human prostate cancer mouse model was used to examine combined androgen ablation and VEGF signaling inhibition. In this model, inhibition of VEGF signaling produced a highly significant inhibition of tumor growth, far exceeding that produced by androgen ablation alone.²³

Resource and Capacity Building

Goal: Maximize the effectiveness and efficiency of prostate cancer scientists by providing them with essential resources and infrastructure for conducting their research.

New and Continued Prostate-Relevant Initiatives

- The Cancer Biomedical Informatics Grid, or caBIG, is a voluntary network (or grid) that connects individuals and institutions to enable the sharing of data and tools, creating a World Wide Web of cancer research. The goal is to speed the delivery of innovative approaches for the prevention and treatment of cancer.
- The Health Information National Trends Survey (HINTS) collects nationally representative information on the public's need for, access to, and use of cancer information. In 2005, NCI developed the HINTS website, which provides the public with access to data from the survey.
- Many of the initiatives discussed in previous sections of this report are providing a range of valuable resources to prostate cancer researchers, including
 - Small Grants Program for Cancer Epidemiology
 - Quick-Trials for Novel Cancer Therapies: Exploratory Grants
 - Activities to Promote Research Collaborations
- The NCI has launched a pilot program to harmonize biospecimen collection and handling through the prostate cancer spores. This pilot will inform NCI's efforts in biospecimens and biobanking across all of its resources and enable a biomarker study of prostate cancer.

Future Research

NCI continues to invest in research that will help meet the goals identified in the *NIH Prostate Cancer Research Plan for FY 2003 – FY 2008*. NCI's major new initiatives—including the NCI Alliance for Nanotechnology in Cancer and programs addressing the relationship among diet, exercise, and cancer—hold tremendous promise for improving and extending the lives of men with prostate cancer. And the numerous active prostate-related clinical trials sponsored by the Institute—often in partnership with other organizations—provide a unique opportunity to identify safer and more effective treatments for the disease and even prevent it from occurring. NCI is a co-convenor of the Prostate Cancer Research Funders, a partnership of public and private organizations that includes the Department of Defense, the Prostate Cancer Foundation, and the

²³ Published in Nicholson B, et al. Combination antiangiogenic and androgen deprivation therapy for prostate cancer: a promising therapeutic approach. *Clin Cancer Res.* 2004 Dec 15;10(24):8728-34.

National Prostate Cancer Coalition, which is working on identifying activities that can be accomplished more effectively as collaborative efforts. The group has already helped develop the Prostate SPORE National Biospecimen Network Pilot Project. Ultimately, this pilot will provide an ongoing platform for the prostate cancer SPOREs to test and validate biomarkers and will enhance the quality and availability of biospecimens to the scientific community. In the coming years, NCI will continue its efforts to ensure that the results of research are translated into practice so that they can truly make a difference in the lives of those affected by prostate cancer.