National Cancer Institute

Colorectal Cancer: Six Years of Research Progress

March 2008

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

Colorectal Cancer: Six Years of Research Progress

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Highlights of NCI's Recent Progress in Colorectal Cancer

Why NCI Performed This Analysis

Background

In 2000, the National Cancer Institute (NCI) convened a multidisciplinary committee of scientists, clinicians, and advocates—the Colorectal Cancer Progress Review Group (PRG)—to review the colorectal cancer research field and make recommendations concerning the most urgent needs and promising directions for future NCI investment. The PRG's report, *Conquering Colorectal Cancer: A Blueprint for the Future,* was issued in April 2000 and provided priority recommendations in six major areas:

- Biology
- Etiology
- Prevention
- Early Detection & Diagnosis
- Treatment & Prognosis
- Cancer Control, Survivorship & Outcomes

Recommendations were also made for the following overarching areas:

- Genetics
- Environment & Lifestyle
- Partnership Platforms
- Imaging
- Behavioral and Health Services Research

Approach

This retrospective analysis performed in 2008 addressed measures of progress such as trends in numbers of NCI-funded colorectal cancer research projects, publications, initiatives, and clinical trials.

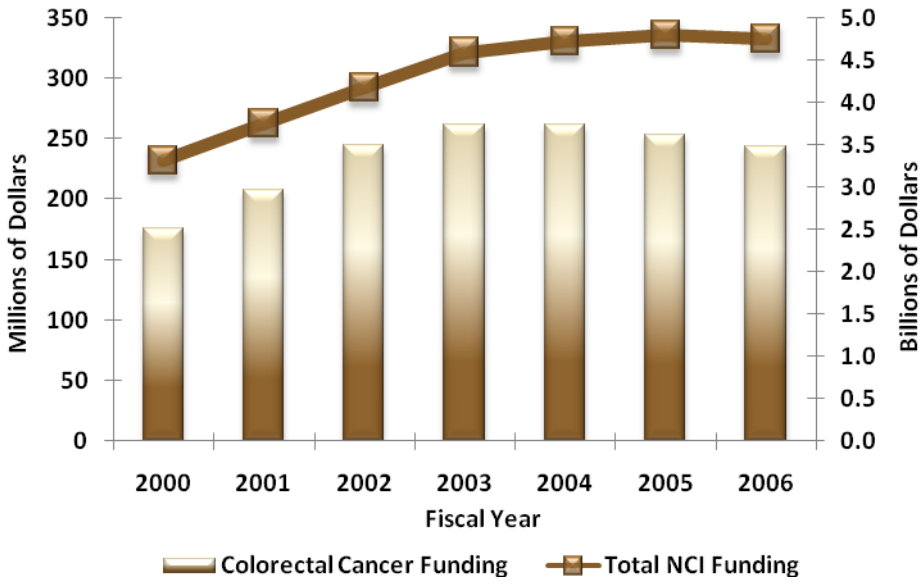
Results

During the past 6 years, NCI funding for colorectal cancer increased by almost 40%. The number of colorectal cancer research projects grew substantially in all of the PRG priority areas.

What NCI Found

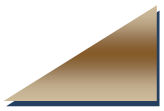
An analysis of NCI's 6-year progress in colorectal cancer found that:

- Since the 2000 Colorectal Cancer PRG report was published, NCI's investment in colorectal cancer grew by 39%, from $175.8 million to $244.1 million.



Progress was also made in the following overarching areas:

Number of Research Projects[1] *(FY2000–FY2006)*



550 Projects 706 Projects

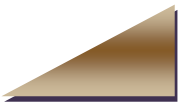
↑ 28%

Number of Investigators with NCI-Funded R01 Grants *(FY2000–FY2006)*

249 Investigators 331 Investigators

↑ 33%

Number of Scientific Articles Acknowledging NCI Support *(CY2000–CY2006)*



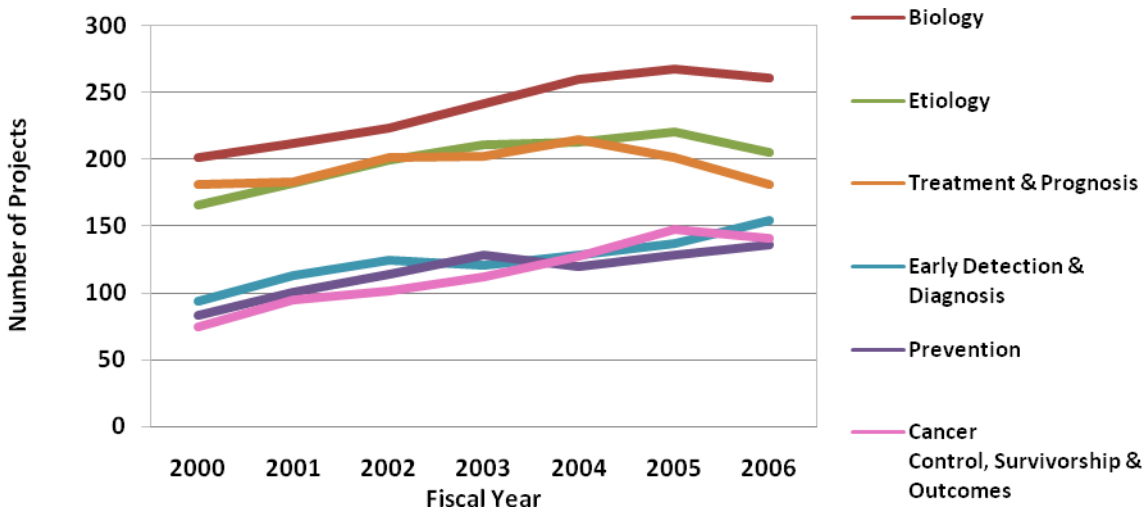
424 Articles 598 Articles

↑ 41%

[1] Research projects included in this analysis had 25% or greater relevance to colorectal cancer. Projects supported by U10 or P30 funding mechanisms and subprojects of Z01 or P50 Specialized Program of Research Excellence (SPORE) programs are not included in the project counts.

Colorectal Cancer Research Projects

Research Projects Addressing Priority Areas Defined by the Colorectal Cancer PRG Increased between FY2000 and FY2006



Additional NCI Activities to Advance Colorectal Cancer Research

Clinical Trials: Between FY2000 and FY2006, 160 NCI-sponsored clinical trials relevant to colorectal cancer were active. The majority of these are treatment trials and most are either Phase I or Phase II trials.

Specialized Programs of Research Excellence: NCI currently supports five SPOREs in gastrointestinal cancers with colorectal cancer components.

Research Highlights

Biology	• More than 200 genes have been identified that are implicated in breast and colorectal cancers. • A subset of epithelial cells has been identified that function as colorectal cancer stem cells.
Etiology	• Abnormal activation of the IGF2 gene is associated with a hereditary risk for colorectal cancer, but it is not associated with any known environmental risk factors for this disease. • People with elevated levels of C-reactive protein, a marker of inflammation, are more than twice as likely to develop colorectal cancer as people who have normal plasma levels of this protein.
Prevention	• Statins, lipid-reducing drugs that are frequently prescribed to treat cardiovascular disease, are effective for chemoprevention of colorectal cancer. • The risk of developing colorectal cancer is not reduced by folic acid, dietary fiber, or the combination of calcium plus vitamin D.
Early Detection & Diagnosis	• Stool assays of selected DNA alterations have shown high sensitivity for cancer (57%–91%) and adenomas. • Research has resulted in refined criteria for diagnosing Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer. These criteria include the level of microsatellite instability in tumors as well as other factors such as age, family history of the disease, genetic analysis, and the biochemical properties of detected tumors.
Treatment & Prognosis	• Patients with metastatic colorectal cancer who received the experimental FOLFOX4 drug regimen (5-fluorouracil/leucovorin/oxaliplatin) lived months longer than those receiving standard chemotherapy. • Compared to standard surgical resection, multivisceral resection for colorectal cancer treatment results in better overall survival.
Cancer Control, Survivorship & Outcomes	• Patients who participated in regular physical activity after being diagnosed with early-to-later stage colorectal cancer reduced their likelihood of cancer recurrence and mortality by 40%–50% or more. • The risk of developing advanced colorectal cancer at a younger age is higher in males and in people who smoke or drink.

THE COLORECTAL CANCER BURDEN

Colorectal cancer is the third most common cancer in the United States among both men and women and accounts for nearly 10% of all cancer deaths. In 2008,[1] an estimated 153,880 individuals will be diagnosed with colorectal cancer, and an estimated 50,640 deaths will occur as a result of this disease. The total number of estimated colorectal cancer cases has increased since 1999 while the number of estimated deaths from this disease has declined slightly in this time (**Figure 1**).

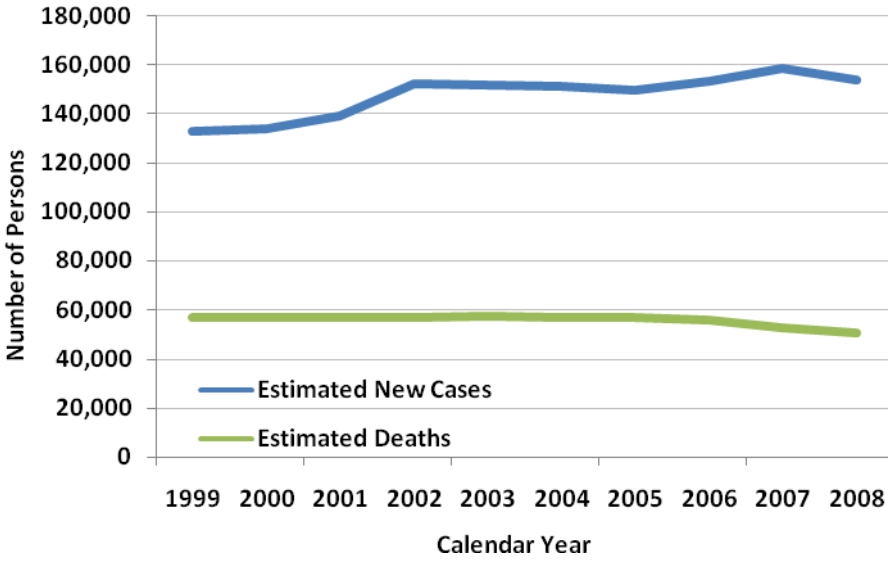


Figure 1. Colorectal Cancer Estimated New Cases and Deaths by Year, 1999 to 2008
Source: American Cancer Society: Cancer Facts and Figures 1999–2008
Available at: http://www.cancer.org/docroot/home/index.asp

The overall incidence rate for colorectal cancer has decreased slightly over the past 20 years (**Figure 2**). Most of this observed decrease reflects lower incidence among whites. Hispanics and Asians/Pacific Islanders are less likely to develop colorectal cancer than blacks or whites, and overall incidence rates in these populations have not changed significantly in recent years. Note that incidence rates are only available for Hispanics, Asians/Pacific Islanders, and American Indians/Alaska Natives from 1995 onward.

[1] Beginning in 2007, estimated new cancer cases were computed using a new model that includes use of data from a much larger percentage of the U.S. population, allowance for geographical variation in cancer incidence, adjustment for delays in reporting, and the inclusion of many socio-demographic, medical facility, lifestyle, and cancer screening behavior variables. This new method produces more accurate estimates of the number of new cancer cases for years and areas for which data are available (see *CA Cancer J. Clin. 2007. Jan-Feb;57(1):30–42*).

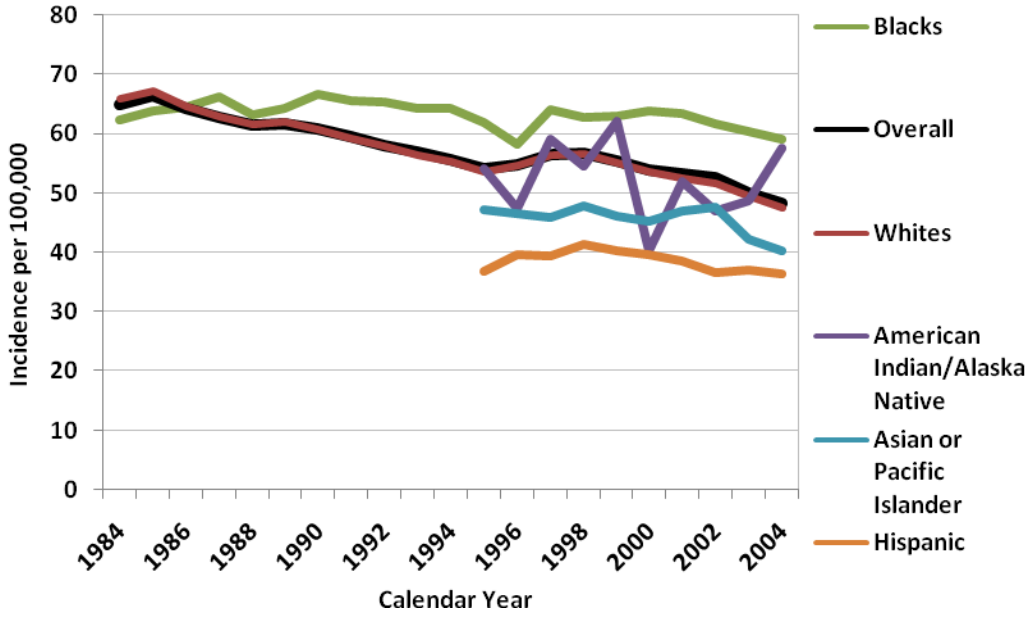


Figure 2. Colorectal Cancer Incidence Rate Trends by Racial/Ethnic Group, 1984 to 2004
Source: NCI's Surveillance, Epidemiology, and End Results (SEER) Program

As shown in **Figure 3**, colorectal cancer incidence rates are higher for males than for females. The causes of this gender disparity are not yet understood.

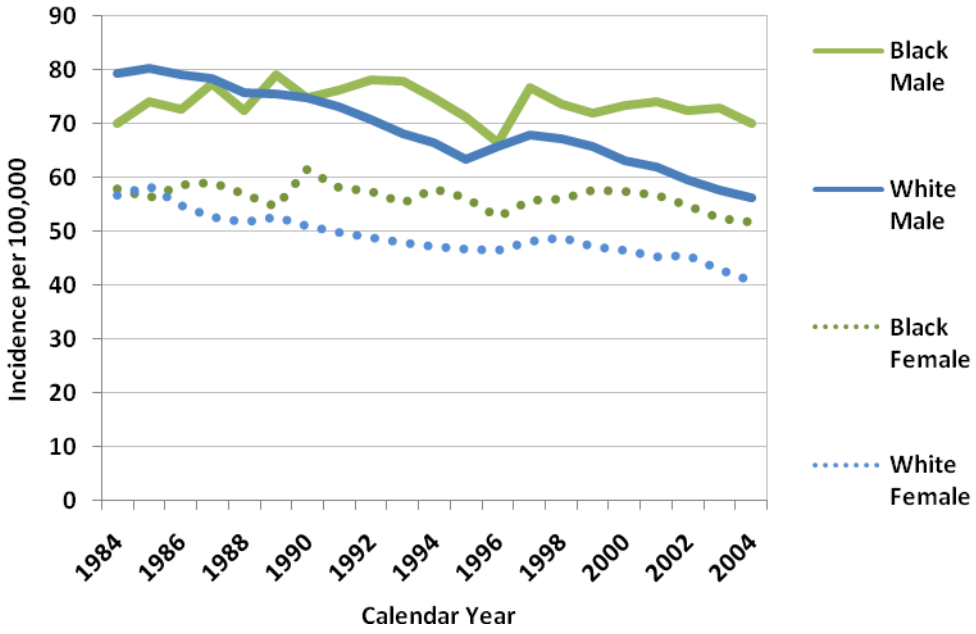


Figure 3. Colorectal Cancer Male–Female Incidence Rate Trends, 1984 to 2004
Source: NCI's Surveillance, Epidemiology, and End Results (SEER) Program

Overall mortality rates for colorectal cancer have declined over the past 20 years for which data are available (**Figure 4**). As shown in **Figure 5**, colorectal cancer mortality rates are higher for males than females. Note that mortality rates are only available for Hispanics, Asians/Pacific Islanders, and American Indians/Alaska Natives from 1995 onward.

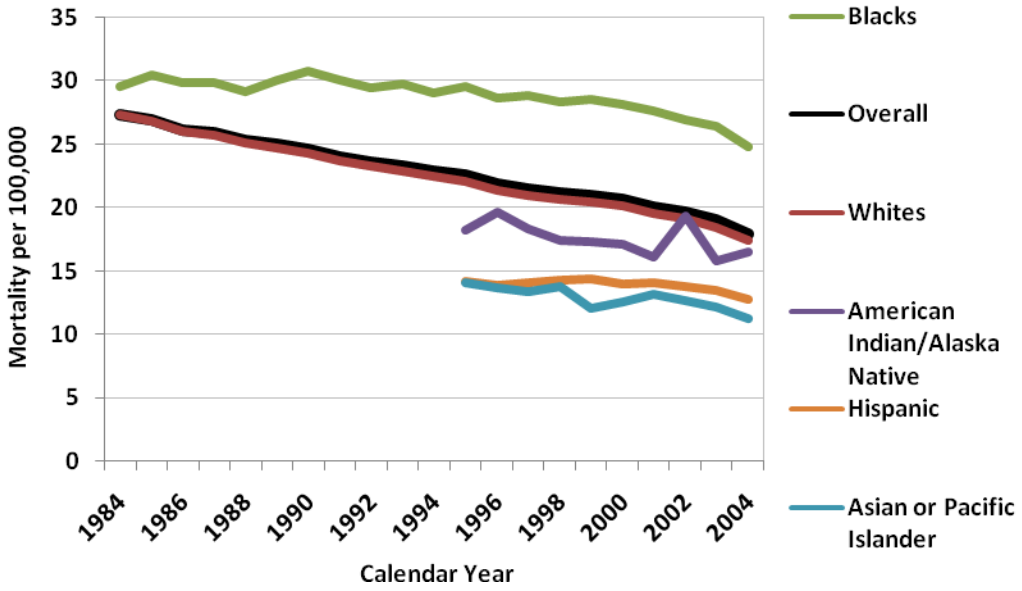


Figure 4. Colorectal Cancer Mortality Rate Trends (All Races), 1984 to 2004
Source: NCI's Surveillance, Epidemiology, and End Results (SEER) Program

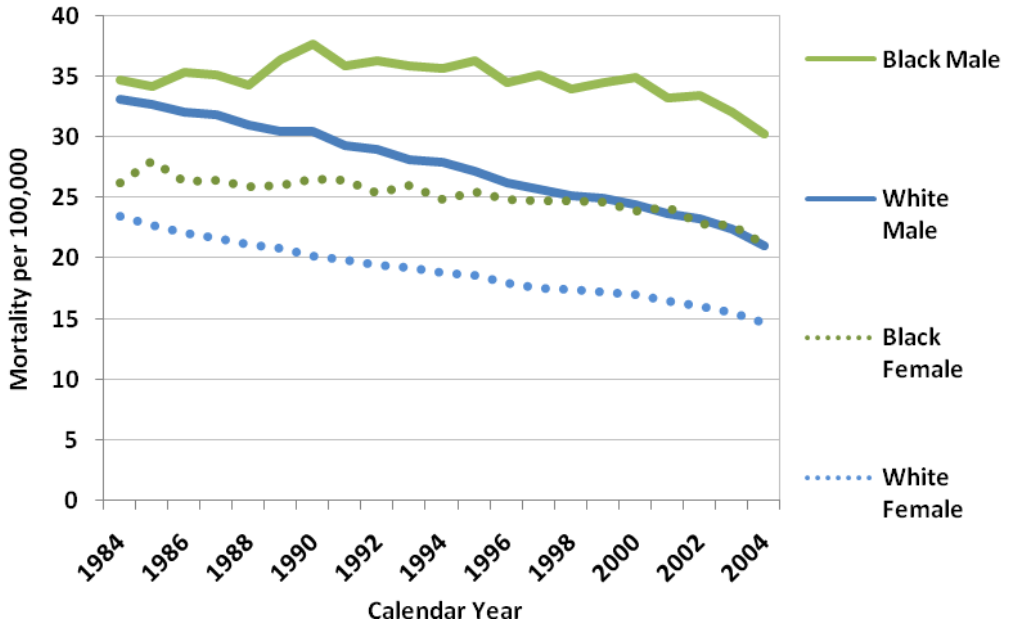


Figure 5. Colorectal Cancer Male–Female Mortality Rate Trends, 1984 to 2004
Source: NCI's Surveillance, Epidemiology, and End Results (SEER) Program

The importance of colorectal cancer screening for people ages 50 and older is supported by multiple research studies and is a priority included in the U.S. Department of Health and Human Services' Healthy People 2010 objectives[2]. National survey results monitor the usage of the recommended colorectal cancer screening tests including fecal occult blood test (FOBT) and endoscopy (including sigmoidoscopy and colonoscopy). **Figure 6** shows that colorectal cancer screening rates, defined as the combined percentage of people who have received a home FOBT in the past 2 years or have ever had a colorectal endoscopy, are on the rise. Regular screening by FOBT or endoscopy has been shown to reduce colorectal cancer deaths.

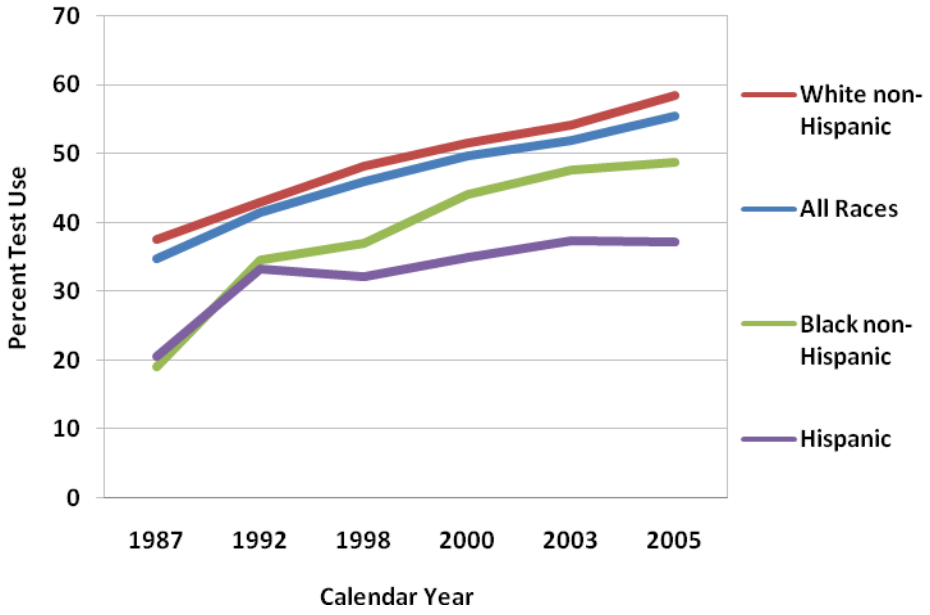


Figure 6. Trends in Colorectal Cancer Screening (FOBT and Endoscopy), 1987 to 2005
Source: Centers for Disease Control and Prevention, National Center for Health Statistics. National Health Interview Survey

[2] Available at http://www.healthypeople.gov/document/HTML/Volume1/03Cancer.htm

NCI PLANNING FOR COLORECTAL CANCER RESEARCH

In 2000, the National Cancer Institute (NCI) convened the Colorectal Cancer Progress Review Group (PRG), a multidisciplinary committee of scientists, clinicians, and advocates, to review the field of colorectal cancer research and identify research priorities to address the most urgent needs and promising directions for future NCI investment. The expertise of the PRG members was complemented by that of approximately 160 additional scientists, clinicians, and advocates who participated in a roundtable meeting on January 5–8, 2000. In April 2000, the Colorectal Cancer PRG issued its report, *Conquering Colorectal Cancer: A Blueprint for the Future.*[3] In this report, the PRG identified research priorities for improving the state of colorectal cancer research in six major scientific areas, including *Biology, Etiology, Prevention, Early Detection and Diagnosis, Treatment and Prognosis,* and *Cancer Control, Survivorship, and Outcomes*. PRG members also developed research priorities related to five overarching and resource-related areas, including *Genetics, Environment and Lifestyle, Partnership Platforms, Imaging,* and *Behavioral and Health Services Research*. For the purposes of this PRG Response Report, the overarching and resource-related recommendations have been folded into the six major scientific areas defined by the PRG. **Table 1** lists all of the PRG research priorities according to the major scientific area they are most closely related to.[4]

Table 1. Recommendations of the Colorectal Cancer PRG

Scientific Area	Research Priorities
Biology	• Define the biological controls for the development of normal and abnormal colorectal epithelial development. • Define the pathways of progression of colorectal neoplasia, including identification of signaling pathways activated in vivo during carcinogenesis.* • Determine whether there are specific tumor genetic subtypes, how these can be linked to histologic type and other known factors, and how knowledge of such subtypes can be used to improve drug development, intervention selection, and prognosis assessment (G).
Etiology	• Support population-based epidemiologic studies, including special populations, which link genetic polymorphisms, diet and lifestyle variables, and endogenous factors with the molecular characteristics of colorectal cancer and its putative precursor lesions. • Validate early and intermediate biomarkers of exposure to environmental influences and genetic polymorphisms. • Re-sequence single nucleotide polymorphism-containing genes involved in carcinogen or hormone metabolism, DNA repair, cell growth control, and immune response and assess their functional polymorphisms in molecular epidemiologic studies in diverse ethnic populations using high-throughput genotyping methods. • Identify the genes that predispose to colorectal cancer, including major and minor alleles of known predisposing genes (G). • Integrate observational screening and interventional approaches in future studies (E). • Improve assessment and characterization of lifestyle and environmental factors (E). • Improve the biological coherence of studies by assessing genetic and environmental factors in studies of the etiology and pathogenesis of colorectal cancer (E).

* This recommendation is a combination of two closely related recommendations from the Biology area.

[3] Available at http://planning.cancer.gov/pdfprgreports/2000colorectal.pdf

[4] In Table 1, the PRG research priorities that originated from the overarching and resource-related chapters are identified with a letter in parentheses according to the following scheme that indicates their origin; (G) = Genetics; (E) = Environment and Lifestyle; (P) = Partnership Platforms; (I) = Imaging; and (B) = Behavioral and Health Services Research.

Scientific Area	Research Priorities
Prevention	• Define pathways that can be targets for nutritional and chemopreventive agent interventions. • Validate the applicability to early clinical trials of surrogate end point biomarkers of colorectal carcinogenesis defined in preclinical animal models. • Conduct studies of combined lifestyle and chemopreventive interventions.
Early Detection & Diagnosis	• Support research into short- to medium-term (5–10-year) strategies for effective implementation of currently recommended methods of early detection at the population level. • Conduct rigorous clinical evaluation of promising markers and modalities, especially in adenoma detection, before their implementation at the population level. • Support developmental research into new markers and modalities and improvements of current methods. • Apply functional and molecular imaging in the selection of screening, surveillance, and treatment strategies to enhance monitoring of chemopreventive and chemotherapeutic responses (I). • Further refine existing and develop novel imaging technologies for the advancement of colorectal cancer screening, staging, and surveillance strategies (I). • Allow for rapid assessment of the benefits and risks of emerging imaging technologies (I).
Treatment & Prognosis	• Enhance local and regional therapy for colorectal cancer by fostering uniform delivery of accepted treatments and the development of new treatment regimens. • Expedite new drug development by identification of intermediate end points and surrogate markers of response that help to define mechanisms of action and predict clinical efficacy. • Discover new indicators of prognosis and the likelihood of response to chemotherapy and radiation. • Determine how relevant gene targets for new therapeutics can be identified (G). • Develop validated markers of biological activity to facilitate clinical trials as part of a strategy to link the development of diagnostics and therapeutics (P). • Foster partnerships among oncologists, gastroenterologists, surgeons, radiologists, and pharmaceutical companies to improve patient access to and facilitate the conduct of clinical trials (P).
Cancer Control, Survivorship & Outcomes	• Conduct studies to identify the best standards of follow-up care after successful treatment of colorectal cancer, focusing attention on which tests give the most information about important outcomes such as resectability, survival, cost, and psychosocial distress. • Develop mechanisms for identifying people at risk for adverse psychological distress and investigate whether psychosocial factors affect compliance with diagnostic and therapeutic regimens and outcomes (e.g., overall survival, cause-specific survival, disease-free survival, and quality of life). • Assess the effectiveness of colorectal cancer screening, prevention, and treatment in elderly and special populations. • Determine how morbidity, quality of life, and mortality are affected by genetic screening and interventions to address human issues (e.g., counseling and disclosure issues) (G). • Develop conceptual models and methods that relate to the efficacy, effectiveness, and cost-effectiveness of intervention strategies, including those that increase the use of effective colorectal cancer prevention, screening, diagnostic evaluation, and treatment modalities, as well as those that enhance the quality of care (B). • Characterize variations in patterns of colorectal cancer prevention, screening, diagnostic evaluation, and treatment, including quality of care for populations, among providers, and in health care systems (B). • Develop and evaluate strategies for improving access to screening, diagnostic evaluation, treatment, and clinical trials and increasing participation in clinical trials of colorectal cancer prevention, screening, diagnostic evaluation, and treatment (B). • Develop and test strategies for increasing the availability of effective colorectal cancer screening, diagnostic evaluation, and treatment methods and opportunities for participation in clinical trials in health care systems (B).

NCI'S INVESTMENT IN COLORECTAL CANCER RESEARCH

NCI Funding for Colorectal Cancer Research

Between FY2000 and FY2006, NCI's investment in colorectal cancer increased by 39% from $175.8 million to $244.1 million (**Figure 7**). The largest increase (18%) occurred in 2002, 2 years after the PRG report was published. These values reflect NCI's total intramural and extramural support for colorectal cancer research, and comprise approximately 5% of the total NCI research budget throughout this time frame.[5]

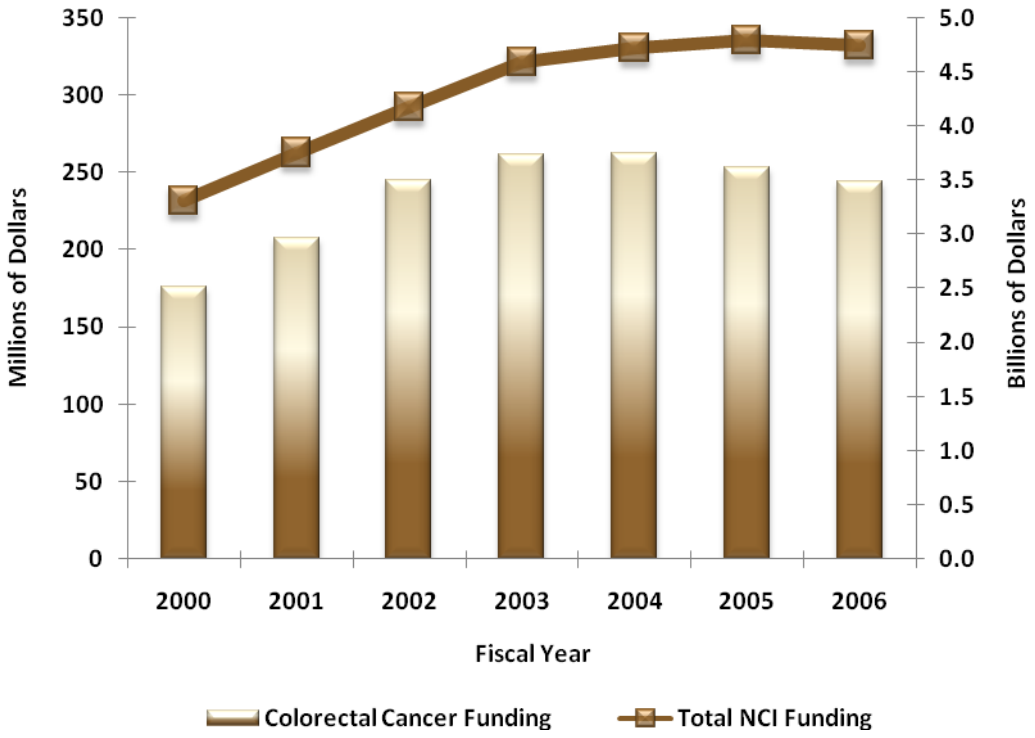


Figure 7. Trends in NCI Funding for Colorectal Cancer Research, FY2000 to FY2006

The majority of the NCI funds designated for colorectal cancer research support the extramural research program. **Figure 8** shows how these research dollars were applied by scientific topic area, as defined by the Common Scientific Outline (CSO), a classification system based on seven broad areas of scientific interest.[6] The greatest percent increase in NCI's investment in colorectal cancer occurred in the category of cancer control, survivorship, and outcomes; spending grew from $13M in FY2000 to $33.4M in FY2006, an increase of 157%.

[5] As reported by NCI's Office of Budget and Finance (NCI Factbook).

[6] To derive these values, dollars associated with each funded extramural project were prorated by estimated colorectal cancer relevance, and this amount was equally distributed into applicable CSO research categories. Colorectal cancer research projects were included regardless of percent relevance to colorectal cancer, except for training grants, which are not included for FY2003–FY2004 because percent relevance was not assigned to training grants in those years.

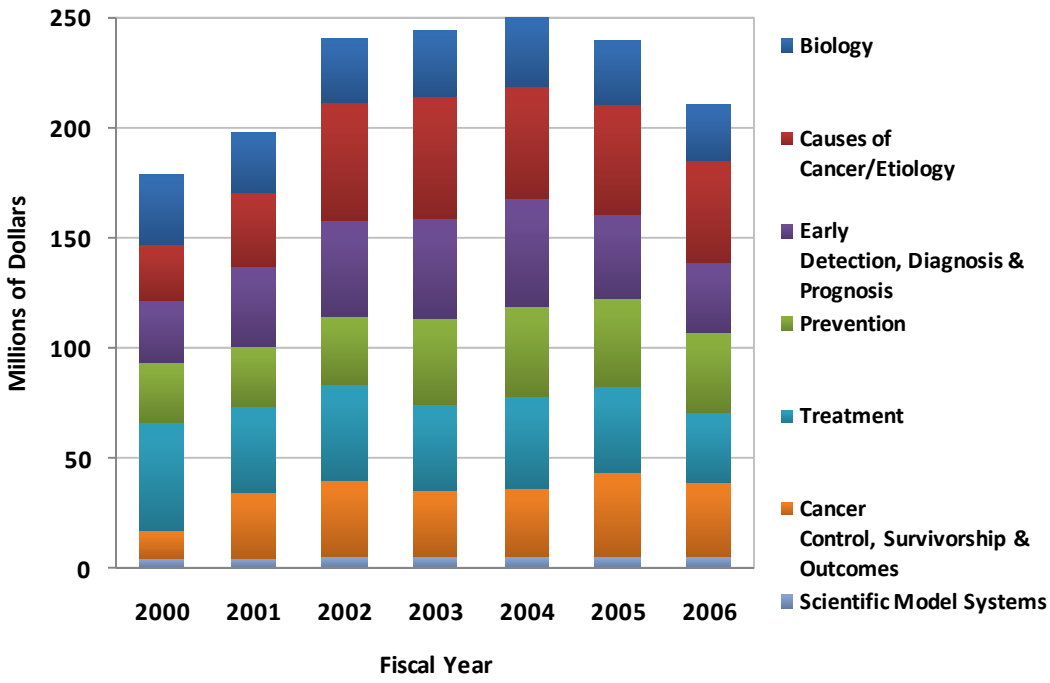


Figure 8. Estimated Funding for Extramural Research by Scientific Area, FY2000 to FY2006

Research Projects

Between FY2000 and FY2006, the number of NCI-sponsored research projects relevant to colorectal cancer increased by 28%, from 550 projects in FY2000 to 706 projects in FY2006. The increase in the NCI-funded colorectal cancer research portfolio is shown in **Figure 9**.[7]

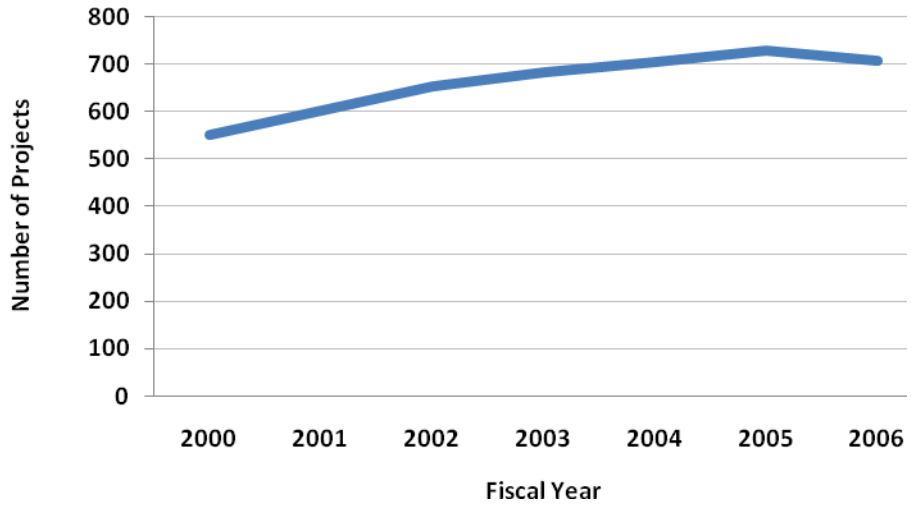


Figure 9. Total Number of NCI-Sponsored Research Projects Relevant to Colorectal Cancer, FY2000 to FY2006

An analysis was performed to determine how NCI's colorectal cancer research portfolio addressed the specific colorectal cancer PRG recommendations in the years following the PRG report. This process involved evaluating each project's scientific abstract to assign relevance to one or more of the research priorities or scientific areas. This process enabled an aggregate analysis of the portfolio according to the six major scientific areas. The results of this analysis are displayed in **Figures 10**, **13**, **14**, **16**, **18**, **20**, and **22**. Many projects were relevant to more than one PRG scientific area and are therefore represented in more than one of these figures.

[7] With the exception of training and intramural projects, research summarized in this graph had 25% or greater relevance to colorectal cancer.

Between FY2000 and FY2006, more colorectal cancer projects were related to biology than to any of the other scientific areas (**Figure 10**). The two scientific areas with the next highest number of related projects were etiology and treatment and prognosis.

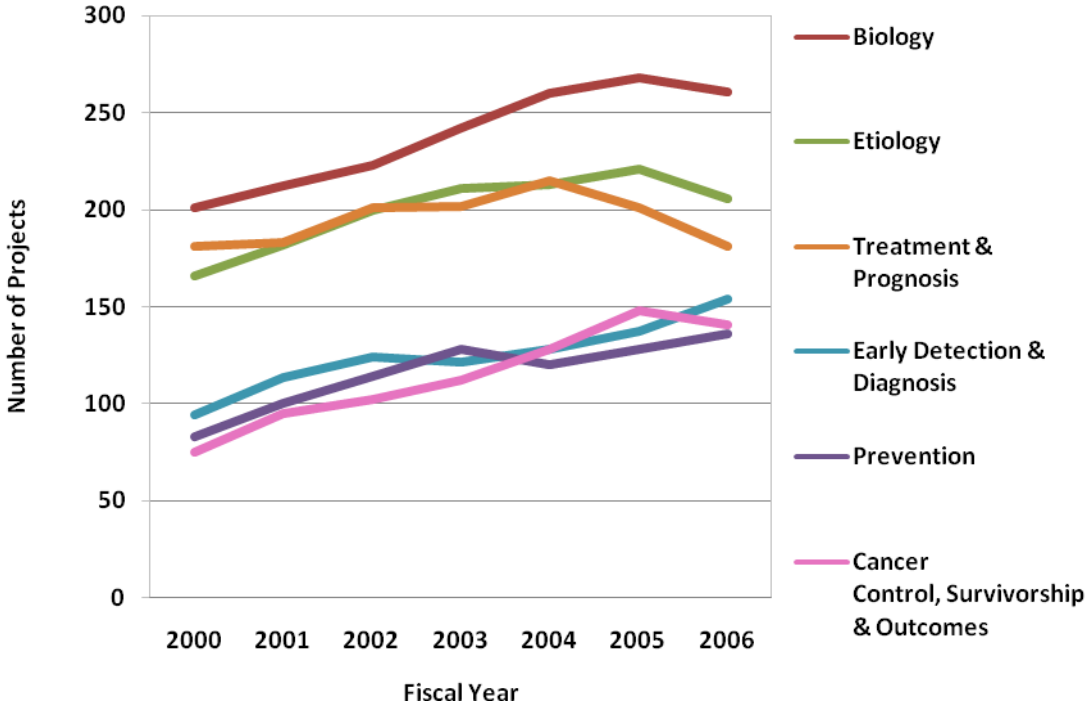


Figure 10. Colorectal Cancer Research by PRG Category, FY2000 to FY2006

Clinical Trials

Between FY2000 and FY2006, NCI sponsored[8] 160 clinical trials relevant to colorectal cancer. The number of active clinical trials each year by trial phase is shown in **Figure 11**.[9] The majority of clinical trials relevant to colorectal cancer focused on treatment, and most of the colorectal cancer trials during this period were either Phase I or Phase II trials. NCI supported 16 studies in the "other" category (no phase specified) during this period. Analyses of clinical trials by type are located in subsequent sections in this report.

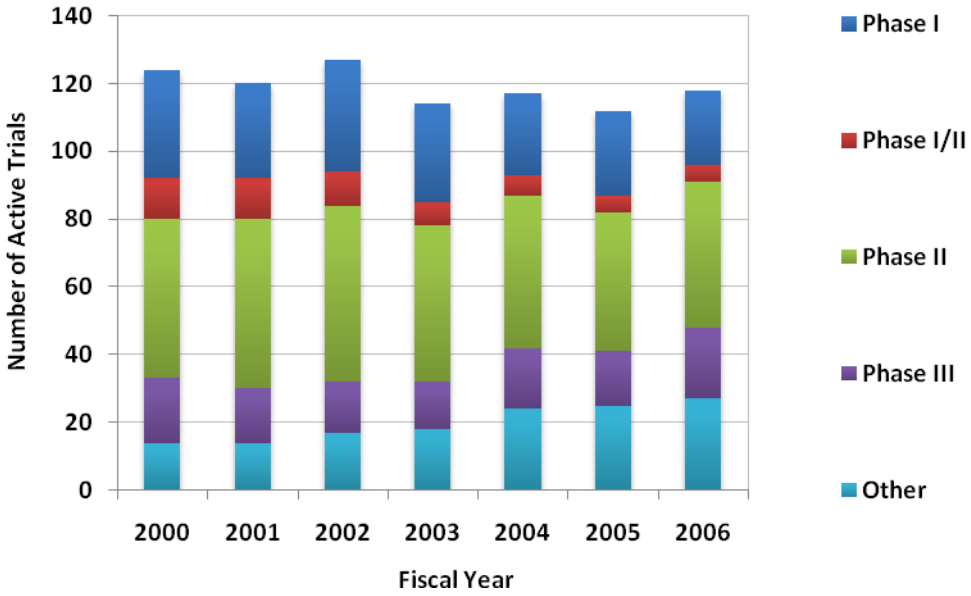


Figure 11. NCI-Sponsored Colorectal Cancer Clinical Trials Active During FY2000 to FY2006

[8] All NCI-sponsored clinical trials in the Physician's Data Query (PDQ) database have been reviewed and approved by NCI's Cancer Therapy Evaluation Program (CTEP) Protocol Review Committee or an approved NCI-designated Cancer Center protocol review and monitoring system, and/or they receive support from an NCI grant or cooperative agreement. All trials included in Figure 11 were active at some point during the fiscal year indicated.

[9] Clinical trials data were retrieved from NCI's PDQ database. Trials performed by NCI's CTEP, Cooperative Groups, Center for Cancer Research, and Division of Cancer Prevention, as well as the European Organization for Research and Treatment of Cancer, are submitted automatically to this database. However, information on trials performed by Cancer Centers and SPOREs and projects funded by the R01, R21, or P01 mechanisms is submitted voluntarily and, therefore, might not be complete.

Specialized Programs of Research Excellence

Specialized Program of Research Excellence (SPORE) grants support specialized centers that promote a bidirectional flow of research, moving basic research findings from the laboratory to clinical settings while also bringing clinical findings back to the laboratory environment. These translational studies often involve cancer patients and populations at risk of cancer and share the common goal of reducing cancer incidence and mortality or improving quality of life. NCI currently supports five P50 specialized center SPORE grants in gastrointestinal cancers that have colorectal cancer components. These SPORE grants, including the titles of their colorectal cancer-relevant subprojects, are detailed in **Table 2**.

Table 2. Gastrointestinal SPORE Grants with Colorectal Cancer-Relevant Projects

Institution	Principal Investigator	Grant Number	Subprojects
Johns Hopkins University	Scott Kern	CA062924	• Diagnosis and prognosis of human cancer through molecular genetic analyses • Risk in familial colorectal cancer • Chemoprevention of human colorectal tumors
University of North Carolina at Chapel Hill	Joel Tepper	CA106991	• Prognostic and predictive factors in outcomes of patients with colorectal cancer: A population-based study • Molecular changes in the NFkB pathway in response to chemoradiation therapy in rectal cancer • Investigation of ERBB signaling in colorectal cancers during liver metastasis • Targeting the RAS>ERK pathway for colorectal cancer treatment • Determination of the role of fucosyltransferases in colorectal cancer initiation and progression
Vanderbilt University	Robert Coffey	CA095103	• Epidermal growth factor receptor (EGFR) axis as a therapeutic target in colorectal cancer • Combined blockade of EGF receptor and COX-2 in intestinal tumorigenesis • Molecular profiling of rectal cancers to evaluate the role of COX-2 • p120 dysfunction in colorectal cancer • Epidemiologic study of predictors for adenoma recurrence
Dana-Farber Harvard Cancer Center	Charles Fuchs	CA127003	• Molecular fluorescent imaging for the early detection of colorectal neoplasms • Defining optimal doses of vitamin D for chemoprevention in blacks • The role of PI3-kinase signaling pathway in defining sensitivity and resistance to anti-EGFR therapy in colorectal cancer
University of Arizona	Eugene Gerner	CA095060	• Genetic variability as prognostic or predictive factors in colorectal intraepithelial neoplasia • MUC1-specific immunotherapy of colon cancer • Redox mechanisms in colorectal cancer • New molecular targets in colorectal and pancreatic cancers

Publications

One indicator of research progress is growth in the number of peer-reviewed publications on a specific topic. The number of colorectal cancer-relevant scientific articles acknowledging NCI support increased from 424 to 598 between calendar years 2000 and 2006 (**Figure 12**), which represents a 41% increase. These values derive from searches of the MEDLINE database[10] for (1) abstracts that included the MeSH term "colorectal neoplasms" and whose authors cited an NCI grant number or author address, (2) abstracts that included variations of the terms "colon" and "rectal" and whose authors cited a gastrointestinal SPORE grant number, and (3) publications retrieved using the Scopus database[11] to identify colorectal cancer publications with an author whose address cited NCI USA. The searches were limited to publications in an English-language, peer-reviewed journal, and both intramural and extramural NCI projects are represented. These values should be considered estimates.

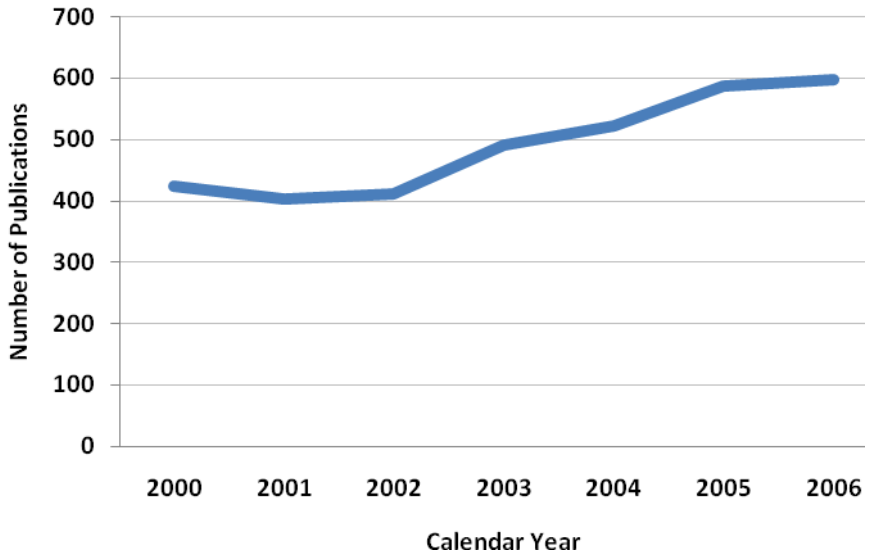


Figure 12. Estimated Number of Scientific Articles on Colorectal Cancer Research Acknowledging NCI Support, 2000 to 2006

[10] Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi
[11] Available at: http://www.scopus.com/scopus/home.url

NCI's Progress in Colorectal Cancer Research

This section describes NCI's progress in addressing research priorities in each of the six scientific areas identified in the Colorectal Cancer PRG report.

Biology

Research Projects

The Colorectal Cancer PRG members identified the following research priorities to improve the understanding of colorectal cancer biology:[12]

- Define the pathways of neoplastic progression.
- Define the biological controls for the development of normal and abnormal colorectal epithelium.
- Determine whether information about the distinct tumor genetic subtypes can be used for drug development, intervention selection, and prognosis assessment.

Between FY2000 and FY2006, there were 440 unique NCI-funded projects that addressed colorectal cancer biology. Analysis of these projects according to how they addressed the PRG research priorities revealed that the majority of them focused on elucidating the pathways of neoplastic progression (**Figure 13**). Thirty-four projects addressed biology-related topics that were not specified by any of the PRG research priorities in this section (shown on the graph as "Other Biology").

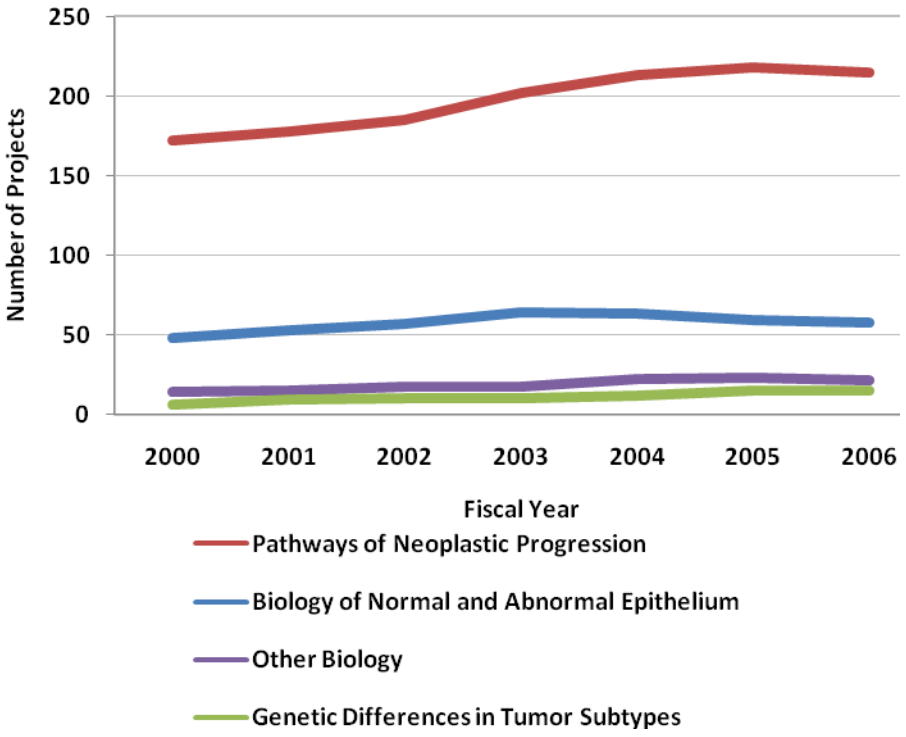


Figure 13. NCI Projects Related to Colorectal Cancer Biology, FY2000 to FY2006

[12] For a more detailed description of these PRG research priorities, please see Table 1 and associated footnotes.

Initiatives

NCI solicits research and develops resources through the use of initiatives that encourage work in priority areas, support multidisciplinary research collaborations, and generate research applications in areas that have not been adequately addressed.

NCI has established the following initiatives related to colorectal cancer biology:

- The **Tumor Microenvironment Network** supports research on the role of the microenvironment and its role in tumor initiation and progression.
  - *Under this request for applications (RFA), NCI funded a study to characterize colon cancer stem cells and stroma.*

- **The Integrative Cancer Biology Program** focuses on the analysis of cancer as a biological system. The cornerstone of the program is development and implementation of computational models of processes relevant to cancer prevention, diagnostics, and therapeutics.
  - *This program was initiated in FY2004. One of the nine Integrative Cancer Biology Program centers is creating a set of DNA repair models that can be used by other centers to facilitate the understanding of cancer therapeutics.*

- The **Stem Cells and Cancer Program** addresses all aspects of stem cell biology, including research on the molecular and biochemical regulation of embryonic and adult stem cell behavior.
  - *NCI has funded one study under this program, which is addressing CD44 expression on colon cancer cells.*

- The **Characterization, Behavior, and Plasticity of Pluripotent Stem Cells Program** supports studies on the characterization, behavior, and plasticity of human and nonhuman stem cells.
  - *This Program Announcement (PA) provided support for one study that is determining the role of transplanted stem cells in colorectal tumor progression.*

- The **Immunoregulation of Gastrointestinal Carcinogenesis Program** addresses the roles of the mucosal immune system in initiating and maintaining inflammatory responses that contribute to the development of premalignant and malignant gastrointestinal cancers and the molecular mechanism(s) by which immunoregulatory cells dampen inflammation and decrease colorectal tumorigenesis.
  - This PA was issued in FY2007. To date, no projects have been funded under this program.

- The **Mouse Models of Human Cancers Consortium** develops, characterizes, and validates mouse models for basic, developmental, and applied cancer research.
  - This RFA has provided support for five studies on mouse models for human colorectal cancer.

- The **High-Impact Pilot Studies in Cancer Biology** focus on new areas that could lead to novel insights into understanding and combating the cancer process.
  - Projects funded under this PA focus on the cardiovascular effects of three anesthetic protocols in mice with colon carcinoma xenografts.

- The **Mouse Proteomic Technologies Initiative** is part of NCI's Clinical Proteomic Technologies for Cancer Program, which is building a foundation of technologies, data, reagents, reference materials, analysis systems, and infrastructure needed to systematically advance our understanding of protein biology in cancer and accelerate discovery research and its clinical applications.
    - This program has developed three colon cancer models, one of them in the years following the release of the Colorectal Cancer PRG Report in 2000.

Research Highlights

Recent results of NCI-sponsored research in the biology of colorectal cancer include the following:

- *Gene Mutations Identified in Colorectal Cancer*

  As part of The Cancer Genome Atlas, researchers isolated and sequenced DNA from over 18,000 genes from human breast and colorectal tumors. They identified nearly 200 mutated genes that may be implicated in these malignancies, most of which were not previously identified as cancer-causing genes.[13]

- *New Insight into Tumor Cell Adaptation to Low Oxygen*

  Oxygen deprivation, or hypoxia, results when the supply of oxygen from the bloodstream does not meet cellular demand. This can occur under normal physiologic conditions as well as in the tumor microenvironment. In both situations, the HIF-1 transcription factor induces a pattern of gene expression that helps the cells adapt to the stressful environment. Two new studies show that HIF-1 does this not only by regulating the supply of oxygen from the bloodstream, but also by actively regulating the oxygen demand of the tissue by reducing the activity of the mitochondria, which consume most of the cellular oxygen.[14,15]

- *Researchers Find Stem Cells in Colorectal Tumors*

  Researchers have identified a subset of epithelial cells that function as colorectal cancer stem cells. These cells are capable of initiating tumor growth when injected into certain strains of mice. These stem cells display an epithelial phenotypic surface marker pattern (EpCAMhigh/CD44+/CD166+) that can be useful for localization or collection purposes.[16]

- *Pathways Mutated in Colorectal Cancer*

  Protein kinases are key components of cell growth regulation pathways, and dysregulation of these enzymes has been implicated in the development of some tumors. Researchers analyzed human colorectal cancer tumors and discovered genetic mutations in eight serine/threonine kinase genes, including three members of the PI3K pathway,[17] a specific pathway regulating cell growth and survival.

- *Scientists Reveal the Actions of a Key Molecular Player in Colorectal Cancer*

  L1-CAM, an adhesion molecule that is usually expressed in neuronal cells, was found at the invasive front of human colon cancer tissue. DNA microarray analysis identified a cluster of genes induced by L1-CAM in a large set of human colon carcinoma tissue samples. These findings suggest the exciting possibility that L1-CAM could be an important target for colon cancer therapy.[18]

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[13] Wood et al. *Science*. 2007. Nov 16;318(5853):1108–1113.
[14] Papandreou et al. *Cell. Metab*. 2006. Mar;3(3):187–97.
[15] Kim et al. *Cell Metab.* 2006. Mar;3(3):177–85.
[16] Dalerba et al. *Proc. Natl. Acad. Sci. USA*. 2007. Jun 12;104(24):10158–63.
[17] Parsons et al. *Nature*. 2005. Aug 11;436(7052):792.
[18] Gavert et al. *Cancer Res*. 2007. Aug 15;67(16):7703–12.

- *Prostaglandin E2 Increases Growth and Motility of Colorectal Carcinoma Cells*
  The Cox-2 enzyme, which is inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, is involved in the synthesis of prostaglandin E2 (PGE2). In this study, researchers dissected the mechanism of PGE2 action in colon cancer invasion and learned that it activates the growth-inducing PI3K signal transduction pathway.[19]

- *Role of Bax in the Apoptotic Response to Anticancer Agents*
  The Bax protein is the prototypic cell death-promoting member of the Bcl-2 protein family. Using colorectal cancer cells with a targeted deletion of this gene, researchers have shown that Bax is required for apoptosis (cell death) mediated by chemopreventive agents such as sulindac, an NSAID, but not for apoptosis mediated by antimetabolic agents such as 5-fluorouracil (5-FU). This finding may lead to improved prevention strategies.[20]

- *Non-Classical (type II) NKT Cells Are Regulators of Tumor Immunosurveillance and Allow Tumor Recurrence*
  Scientists have been working to understand why antitumor responses induced by cytotoxic T lymphocytes (CTLs) in cell culture do not always translate to tumor regression in vivo. Using a colon carcinoma model, researchers determined that of all the types of immunoregulatory T cells, only the CD1-restricted type II natural killer T-cells are required for the immune suppression that hinders tumor regression in animals. These findings have implications for the development of novel strategies for harnessing the immune system to improve tumor regression in humans with colorectal cancer.[21]

[19] Sheng et al. *J. Biol. Chem.* 2001. May 25;276(21):18075–81.
[20] Zhang et al. *Science*. 2000. Nov 3;290(5493):989–92.
[21] Terabe et al. *J. Exp. Med.* 2005. Dec 19;202(12):1627–33.

Etiology

Research Projects

The Colorectal Cancer PRG members identified the following research priorities to improve the understanding of colorectal cancer etiology:[22]

- Perform population studies linking genetic, lifestyle, and molecular factors.
- Identify colorectal cancer susceptibility genes.
- Improve assessment of gene-environment interactions in etiology and pathogenesis.
- Characterize lifestyle and environmental risk factors.
- Integrate screening and intervention approaches to identify risk factors.
- Characterize functional gene polymorphisms.
- Validate genetic and environmental biomarkers.

Between FY2000 and FY2006, there were 384 unique NCI-funded projects that addressed colorectal cancer etiology. Most of the projects relevant to etiology focused on the PRG priority that addressed population studies designed to link genetic and lifestyle variables with the molecular characteristics of colorectal cancer (**Figure 14**). The number of projects addressing etiology topics not specified by a particular PRG priority ("Other Etiology") remained relatively constant during these years.

[22] For a more detailed description of these PRG research priorities, please see Table 1 and associated footnotes.

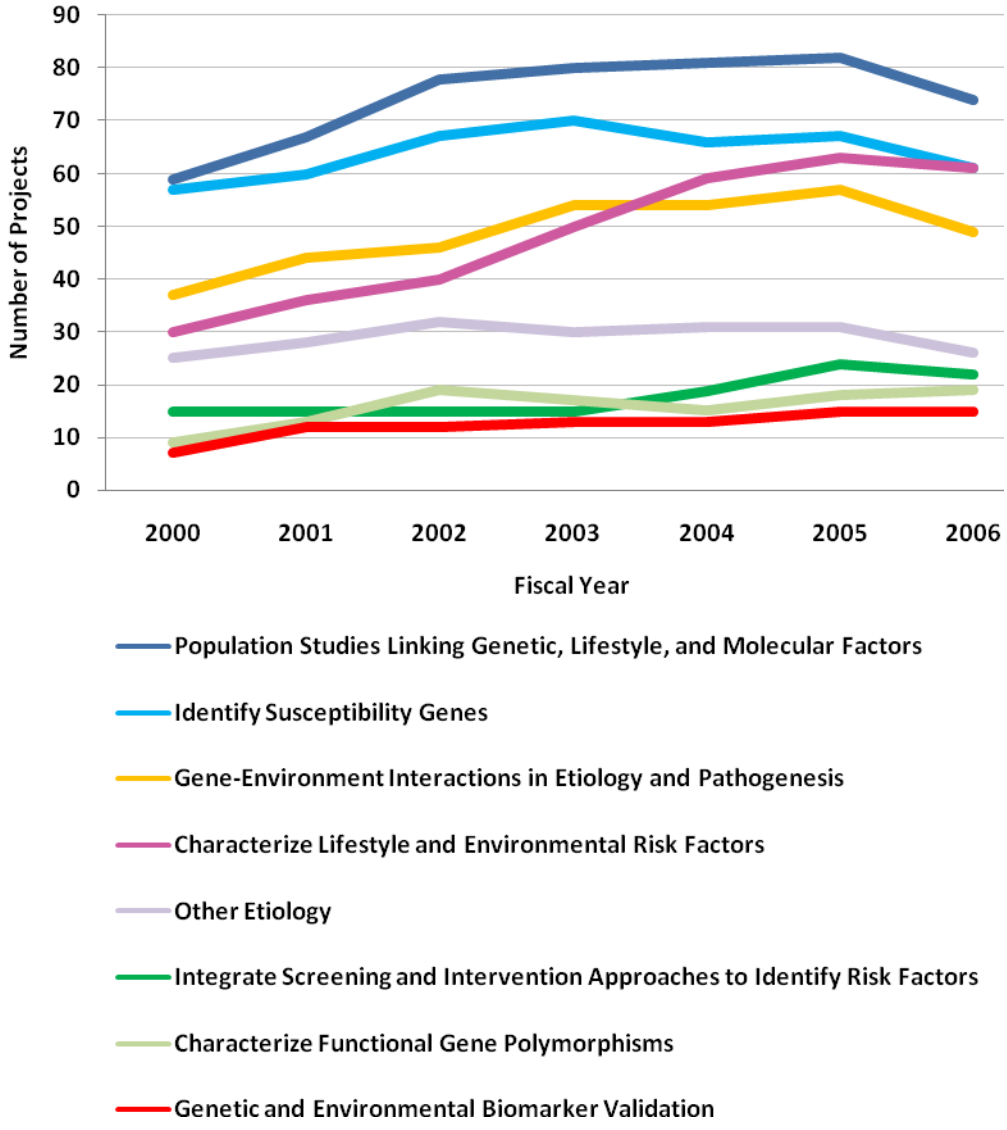

Figure 14. NCI Projects Related to Colorectal Cancer Etiology, FY2000 to FY2006

Clinical Trials

Between FY2000 and FY2006, NCI sponsored 13 clinical trials related to colorectal cancer etiology (**Figure 15**). These included studies focused on the genetics, natural history, and epidemiology of colorectal cancer. Clinical studies that addressed colorectal cancer genetics included studies of genes that predispose to colorectal cancer as well as genes that predict treatment response. Trials that focused on natural history/epidemiology addressed the long-term effects and outcomes following treatment for colorectal cancer.

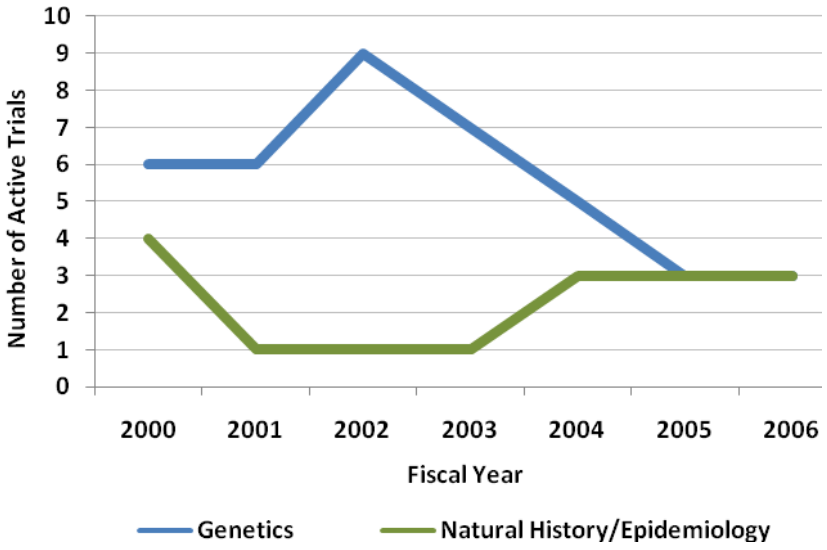

Figure 15. NCI Clinical Trials Related to Colorectal Cancer Etiology, FY2000 to FY2006

Initiatives

NCI has issued the following research initiatives related to colorectal cancer etiology:

- The **Transdisciplinary Research on Energetics and Cancer (TREC) Centers** foster collaboration among transdisciplinary teams of scientists to accelerate progress toward reducing the cancer incidence, morbidity, and mortality associated with obesity, low levels of physical activity, and poor diet.
  - *The four TRECs are examining the relationship between obesity and colorectal cancer.*

- The **Diet, Epigenetic Events, and Cancer Prevention** program promotes innovative preclinical and clinical research to determine how diet and dietary factors affect epigenetic processes involved in cancer prevention.
  - *Four colorectal cancer projects have been funded under this program, including studies of the molecular epidemiology of colorectal cancer subtypes, epigenomic influences of diet on intestinal neoplasia, and impact of diet and DNA methylation in colon mucosa and adenomas.*

- The **Immunoregulation of Gastrointestinal Carcinogenesis Program** addresses the roles of the mucosal immune system in initiating and maintaining inflammatory responses that contribute to the development of premalignant and malignant gastrointestinal cancers and the molecular mechanism(s) by which immunoregulatory cells dampen inflammation and decrease colorectal tumorigenesis.
  - *This PA was issued in FY2007. To date, no colorectal cancer projects have been funded under this program.*

- The **Small Grants Program for Cancer Epidemiology** supports pilot projects, tests of new techniques, and innovative or high-risk research.
  - *NCI has supported 28 studies on colorectal cancer epidemiology through this PA, including studies of prostaglandin synthesis and colorectal cancer risk, the association between polymorphisms in key genes of the calcium-vitamin D pathway and colorectal cancer risk, and an evaluation of the biological relevance of choline intake.*

- The **Colon Cancer Family Registry** is an international research infrastructure for investigators conducting population- and clinic-based interdisciplinary studies on the genetic and molecular epidemiology of colon cancer and its behavioral implications.
  - *The Colon Cancer Family Registry has information and biospecimens contributed by more than 11,300 families across the colon cancer risk spectrum and from population-based or relative controls.*

- The **Ubiquitin and Ubiquitin-Like Modifications Regulating Disease Processes** program elucidates the roles of ubiquitin and ubiquitin-like modifications in development, normal physiology, and/or disease progression.
  - *NCI has funded three colorectal cancer studies under this PA on topics including the role of Crd-Bp-regulated mRNA stability in colorectal cancers, beta-catenin regulation by tumor suppressor adenomatous polyposis coli (APC), and the roles of ubiquitin C-terminal hydrolase L1 in colorectal cancer progression.*

Research Highlights

Recent results of NCI-sponsored research in the etiology of colorectal cancer include the following:

- *Genetic Markers of Colorectal Cancer Risk Identified*

  Two NCI-funded genome-wide association studies have identified a locus on chromosome 8 (8q24) in which several single nucleotide polymorphisms—changes in a single nucleotide of DNA—are associated with significantly increased risk of colorectal cancer. Interestingly, this locus has also been implicated in prostate cancer.[23]

- *Loss of IGF2 Imprinting: A Potential Marker of Colorectal Cancer Risk*

  Genomic imprinting is a form of gene silencing caused by heritable DNA modifications. Loss of genomic imprinting (LOI), of the insulin-like growth factor II gene (IGF2) involves activation of the normally silent maternally inherited allele. In the current study, researchers determined that LOI of IGF2 is associated with a hereditary risk for colorectal cancer, but it is not associated with any known environmental risk factors for this disease (e.g., tobacco, alcohol, NSAIDs, and certain nutrients).[24]

- *Environmental and Heritable Factors in the Causation of Cancer—Analyses of Cohorts of Twins from Sweden, Denmark, and Finland*

  The contribution of hereditary factors to the causation of sporadic cancer is unclear. In this study, researchers assessed the risk of several types of cancer in 44,788 pairs of European twins. Results showed that heritable factors only accounted for 35% of the colorectal cancer cases in these populations, indicating that environmental factors play an important role in the development of sporadic cancers.[25]

- *Population-Based Molecular Detection of Hereditary Nonpolyposis Colorectal Cancer*

  Researchers have developed a large-scale molecular screening approach for detecting colorectal cancer in individuals at risk for hereditary nonpolyposis colorectal cancer (HNPCC). The two-step screening approach is based on microsatellite instability (MSI) patterns and genetic mutations in the MSH2 and MLH1 genes that are characteristic of individuals afflicted with HNPCC.[26]

- *Tumor Suppressor Gene Analysis May Yield New Targeted Therapies*

  Scientists performed a mutational analysis of the tyrosine phosphatase gene superfamily in human cancers. These genes encode key intracellular signaling molecules that are involved in various processes including growth and proliferation. Seventy-seven somatic mutations were found in six known tyrosine phosphatases that affected more than 25% of all colorectal cancers. The mutations reduced or eliminated the function of the phosphatase proteins for which they code, thereby hampering the ability of the proteins to regulate cellular functions such as growth, differentiation, death, and tissue invasion.[27]

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[23] Zanke et al. *Nat. Genet.* 2007. Aug;39(8):989–94.
[24] Cruz-Correa et al. *Gastroenterology.* 2004. Apr;126(4):964–70.
[25] Lichtenstein et al. *N. Engl. J. Med.* 2000. Jul 13;343(2):78–85.
[26] Salovaara et al. *J. Clin. Oncol.* 2000. Jun;18(11):2193–200.
[27] Wang et al. *Science.* 2004. May 21;304(5674):1164–6.

- *C-Reactive Protein Linked to Increased Risk of Colon Cancer*

  Inflammation is a known risk factor for the development of colorectal cancer, and use of anti-inflammatory drugs (e.g., NSAIDS) can reduce colorectal cancer risk. A recent study showed that people with elevated levels of C-reactive protein, a marker of inflammation, are more than twice as likely to develop colorectal cancer as people who have normal plasma levels of this protein.[28]

- *Gene Inactivation May Indicate Colon Cancer "Field Defect"*

  Sporadic colorectal cancers often arise from a region of unstable, potentially precancerous cells referred to as a "field defect." Researchers have linked the development of this precancerous state to an epigenetic process called DNA promoter methylation. In the current study, methylation of the MGMT gene was observed in nearly half of the tumors and in up to 94% of the apparently normal surrounding mucosa (up to 10 cm away). The findings indicate that MGMT methylation may be useful as a marker of risk for developing colon cancer.[29]

- *Prostate Irradiation Increases Risk of Rectal Cancer*

  Findings from a retrospective cohort study indicate that, among men who have been treated for prostate cancer, those who received radiation are at a slightly higher risk of subsequently developing rectal cancer than men who were treated with surgery alone.[30]

- *BRCA2 Mutations and Risk of Colorectal Cancer*

  Germline mutations of the BRCA1 and BRCA2 genes have been implicated in the development of breast and ovarian cancers. A recent population-based study showed that the risk of developing colorectal cancer was increased threefold for relatives of ovarian cancer patients who have a known mutation in the BRCA2 gene.[31]

[28] Erlinger et al. *JAMA.* 2004. Feb 4;291(5):585–90.
[29] Shen et al. *J. Natl. Cancer Inst.* 2005. Sep 21;97(18):1330–8.
[30] Baxter et al. *Gastroenterology*. 2005. Apr;128(4):819–24.
[31] Risch et al. *Am. J. Human Genet.* 2001. Mar;68(3):700–10.

Prevention

Research Projects

The Colorectal Cancer PRG members identified the following research priorities to improve the understanding of colorectal cancer prevention:[32]

- Define pathways that can be targets of nutritional and chemoprevention interventions.
- Conduct studies of combined lifestyle and chemopreventive interventions.
- Validate surrogate end point biomarkers of carcinogenesis in preclinical studies.

Between FY2000 and FY2006, there were 279 unique NCI-funded projects that addressed colorectal cancer prevention. Most of the projects relevant to prevention during this time frame focused on the PRG priority that addressed targets for nutritional and chemopreventive intervention (**Figure 16**). The PRG report did not contain a research priority that addressed a single intervention modality only (e.g., lifestyle intervention only or chemoprevention only). However, a large proportion of NCI's research portfolio in the past 6 years focused on single intervention modalities. These projects are represented in the category called "Other Prevention" in **Figure 16**.

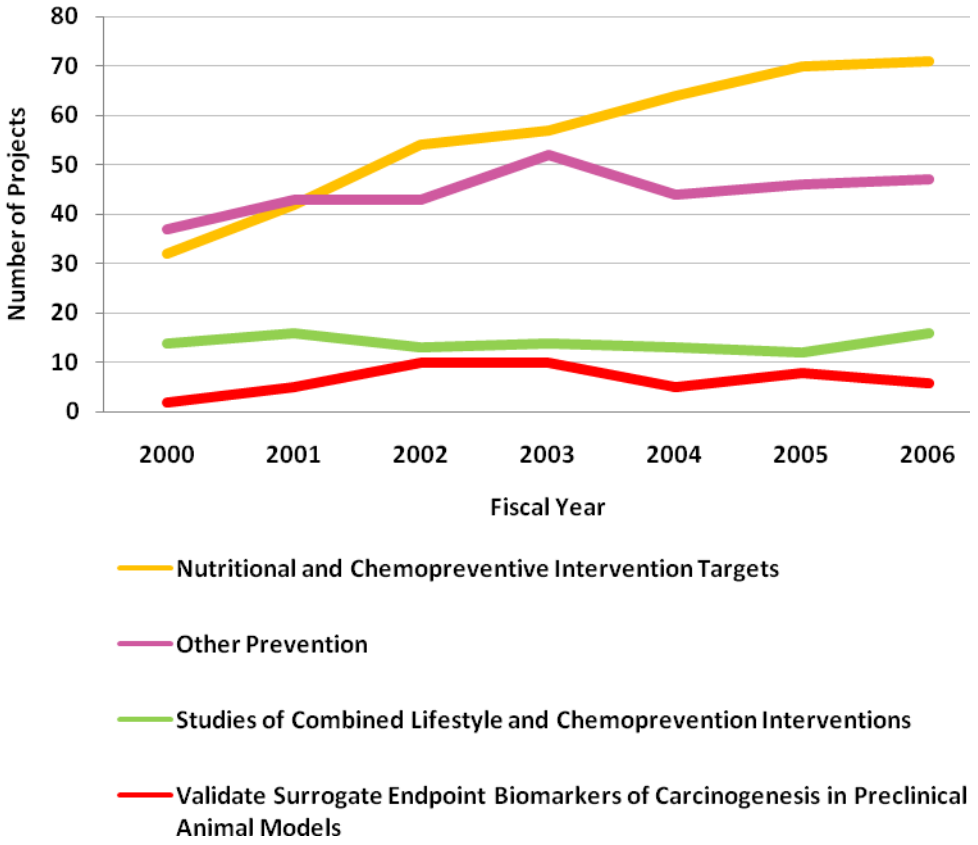

Figure 16. NCI Projects Related to Colorectal Cancer Prevention, FY2000 to FY2006

[32] For a more detailed description of these PRG research priorities, please see Table 1 and associated footnotes.

Clinical Trials

NCI sponsored 18 clinical trials in colorectal cancer prevention between FY2000 and FY2006. The number of NCI-sponsored clinical trials related to colorectal cancer prevention (**Figure 17)** has increased in recent years with the largest increase occurring between FY2005 and FY2006. Examples of prevention trials include studies of chemoprevention or nutritional prevention approaches for individuals with a genetic predisposition to colorectal cancer or individuals who have been previously treated for colorectal adenomas or adenocarcinomas.

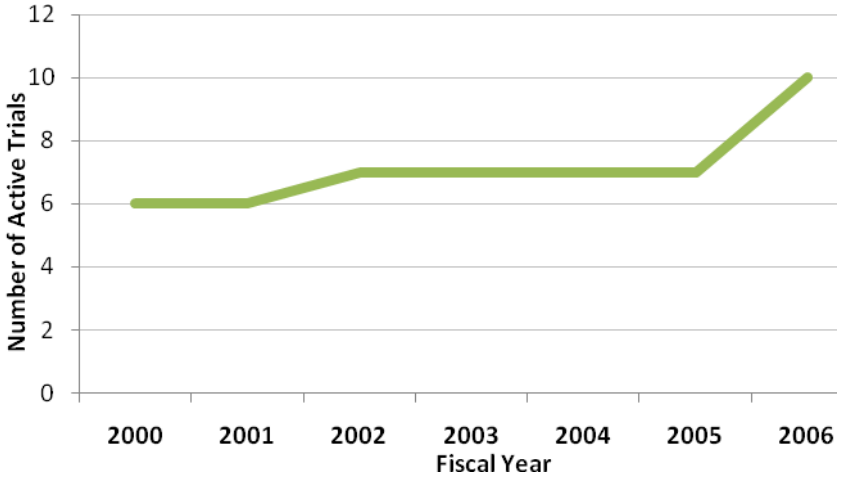

Figure 17. NCI Clinical Trials Related to Colorectal Cancer Prevention, FY2000 to FY2006

Initiatives

NCI has established the following initiatives related to colorectal cancer prevention:

- The **Early Phase Prevention Trials Consortia** are working to accelerate the development of safe and effective cancer prevention drugs.
  - *This program currently supports three colorectal cancer prevention clinical trials.*

- The **National Surveys of Colorectal Cancer Screening Policies and Practices** has collected nationally representative data on physician and health system factors that influence the use of screening and diagnostic follow-up for the early detection of colorectal cancer in community practice.
  - *NCI launched the National Survey of Colorectal Cancer Screening Practices in 1999 in collaboration with the Centers for Disease Control and Prevention and the Centers for Medicare and Medicaid Services. The Survey of Health Plan Policies and Programs for Colorectal Cancer Screening was fielded between November 2005 and April 2006.*

- The **Cancer Prevention Research Small Grant Program** supports developmental research in chemoprevention agent development, biomarkers, early detection, and nutrition science.
  - *Under this initiative, NCI has provided support for 48 colorectal cancer studies, including research on a novel sulindac derivative for colon cancer chemoprevention, the effect of digestion on the cancer chemopreventive activity of tea catechins, and studies of nucleoside transport inhibitors for cancer prevention.*

- The **Cancer Prevention, Control, Behavioral, and Population Sciences Career Development Award** supports specialized didactic study and mentored research in scientific areas relevant to cancer prevention, cancer control, and behavioral and population sciences research.
  - *NCI has supported 16 colorectal cancer projects through this PAR, including studies on the relationship of hormones and hormone-related genes to colorectal cancer, colorectal cancer screening in various populations, and genetic testing for hereditary cancer syndromes.*

- The **Diet-Induced Changes in Inflammation as Determinants of Colon Cancer** initiative supports innovative research to identify and characterize diet-induced changes in inflammation and colon cancer risk.
  - *This initiative has supported two colorectal cancer studies since the release of the PRG. One study focuses on the benefits of a Mediterranean diet for colon cancer prevention and another examines the ability of bromelain to prevent inflammatory bowel disease-associated colon cancer.*

- The **International Cancer Screening Network** is a voluntary consortium of countries with active population-based cancer screening programs.
  - *The consortium was established in December 1988. In 2006, it created an inventory of colorectal cancer screening activities in consortium member countries.*

- The **Community Clinical Oncology Program (CCOP)** links community cancer specialists, primary care physicians, and other health care professionals to the NCI-supported Cooperative Groups and Cancer Centers to conduct NCI-approved cancer treatment, prevention, and control clinical trials.
  - *NCI established the CCOP in 1983. The Institute currently supports 50 CCOPs and 13 minority-based CCOPs across the country. Prevention clinical trials led by the CCOP include the Colorectal Adenoma Prevention Study, which showed that daily aspirin use can reduce the development of adenomas in patients who have had colorectal cancer previously.*

- The **Prevention Agents Program** is part of the Chemopreventive Agent Development Research Group, which provides scientific and administrative oversight for preclinical chemoprevention agent development up to early Phase I research using physiological end points in healthy volunteers.
  - *The program includes 13 agents under investigation to prevent colon cancer.*

- The **Innovative and Exploratory Research in Digestive Diseases and Nutrition** program stimulates the application of highly novel approaches for studying digestive diseases (including associated cancers) and nutrition.
  - *This PA has provided support for seven colorectal cancer studies, including research on the role of the extracellular calcium-sensing receptor in dietary calcium chemoprevention and how dietary vitamin A (retinol) inhibits colorectal cancer progression.*

Research Highlights

Recent results of NCI-sponsored research in colorectal cancer prevention include the following:[33]

- *The Effect of Celecoxib, a Cyclooxygenase-2 Inhibitor, in Familial Adenomatous Polyposis*

  Patients with familial adenomatous polyposis (FAP) have a nearly 100% risk of colorectal cancer in their lifetimes. These individuals develop hundreds or thousands of precancerous colorectal polyps that eventually become malignant. The cyclooxygenase-2 inhibitor celecoxib was tested on patients with FAP to determine if it could reduce the number of polyps in these individuals. The trial showed that patients who received daily celecoxib (800 mg) demonstrated a significant reduction in the number of colorectal polyps compared to placebo controls.[34]

- *Celecoxib Significantly Reduces the Risk of Precancerous Colorectal Polyps*

  A recent Phase III clinical trial established that celecoxib can significantly reduce the development of colorectal polyps in patients who have previously developed spontaneous adenomas. Unfortunately, the authors also reported a significant dose-dependent increase in serious cardiovascular events in participants taking celecoxib. Furthermore, a recent safety review found that participants had an increased risk of serious cardiovascular events—cardiovascular death, heart attack, stroke, or heart failure—if they took celecoxib (Celebrex) daily for approximately 3 years. These results indicate that further study is needed before celecoxib can be recommended for prevention of spontaneous colorectal adenomas.[35, 36]

- *A Randomized Trial of Aspirin to Prevent Colorectal Adenomas*

  Two randomized, double-blind trials were conducted to determine the effect of aspirin on the incidence of colorectal adenoma in patients with a history of adenomas or colorectal cancer. Both studies showed that daily use of aspirin (81 mg or 325 mg) is associated with a significant reduction in the incidence of colorectal adenomas in these patients compared to controls.[37, 38]

- *Folic Acid Study Shows Surprising Results*

  Laboratory and epidemiological data suggest that folic acid may have an antineoplastic effect in the large intestine. The chemopreventive potential of folic acid was tested on a cohort of patients with a history of colorectal adenoma. Surprisingly, the study revealed that daily intake of folic acid (1 mg) actually increased, rather than decreased, the likelihood of developing adenoma compared to placebo.[39]

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[33] While not all of the clinical trials featured in the "Research Highlights" section are fully funded by the NCI, the resulting publications summarized here do cite NCI support.
[34] Steinbach et al. *N. Engl. J. Med.* 2000. Jun 29;342(26):1946–52.
[35] Bertagnolli et al. *N. Engl. J. Med.* 2006. Aug 31;355(9):873–8.
[36] Solomon et al. *N. Engl. J. Med.* 2005. Mar 17;352(11):1071–80.
[37] Sandler et al. *N. Engl. J. Med.* 2003. Mar 6;348(10):883–90.
[38] Baron et al. *N. Engl. J. Med.* 2003. Mar 6;348(10):891–9.
[39] Cole et al. *JAMA.* 2007. Jun 6;297(21):2351–9.

- *High-Fiber Cereal Does Not Affect Recurrence of Colorectal Adenomas*

  Evidence suggests that dietary factors, such as cereal fiber, may mediate the risk of developing colorectal cancer. A randomized trial tested whether dietary supplementation with wheat-bran fiber reduces the rate of recurrence of colorectal adenomas. Results of the trial showed that consumption of high amounts of dietary fiber had no significant effect on the risk of developing colorectal cancer compared to low-fiber control groups.[40]

- *More Evidence Links Statins to Cancer Prevention*

  Statins, lipid-reducing drugs that are frequently prescribed to treat cardiovascular disease, are known to inhibit the growth of colon cancer cells. A large case-control study found that people who took statins for at least 5 years had a 47% lower rate of developing colorectal cancer than control subjects who did not take these drugs.[41]

- *Calcium Plus Vitamin D Does Not Reduce Colorectal Cancer Risk*

  Higher intake of calcium and vitamin D has been associated with a reduced risk of colorectal polyp recurrence in secondary prevention trials. A randomized, double-blind trial was performed to determine if calcium plus vitamin D can reduce the risk of developing primary colorectal cancer in postmenopausal women. After 7 years, the study found no significant difference between the group of women taking calcium and vitamin D compared to controls taking placebo. Ongoing studies are assessing the long-term effect of this potential intervention.[42]

[40] Alberts et al. *N. Engl. J. Med.* 2000. Apr 20;342(16):1156–62.
[41] Poynter et al. *N. Engl. J. Med.* 2005. May 26;352(21):2184–92.
[42] Wactawski-Wende et al. *N. Engl. J. Med.* 2006. Feb 16;354(7):684–96.

Early Detection and Diagnosis

Research Projects

The Colorectal Cancer PRG members identified the following research priorities to improve the understanding of colorectal cancer early detection and diagnosis:[43]

- Develop biomarkers and imaging modalities for early detection.
- Assess implementation of colorectal cancer screening strategies.
- Conduct rigorous clinical evaluation of early detection markers for screening.
- Refine existing and develop novel imaging technologies to advance screening, staging, and surveillance.
- Apply functional and molecular imaging to monitor response to chemoprevention or chemotherapy.
- Assess emerging imaging technologies.

Between FY2000 and FY2006, there were 294 unique NCI-funded projects that addressed the early detection and diagnosis of colorectal cancer. Most of the projects relevant to this category focused on the PRG priority that addressed the development of biomarkers and imaging modalities for early detection (**Figure 18**). Between FY2000 and FY2006, project counts increased for all PRG priorities related to colorectal cancer early detection and diagnosis.

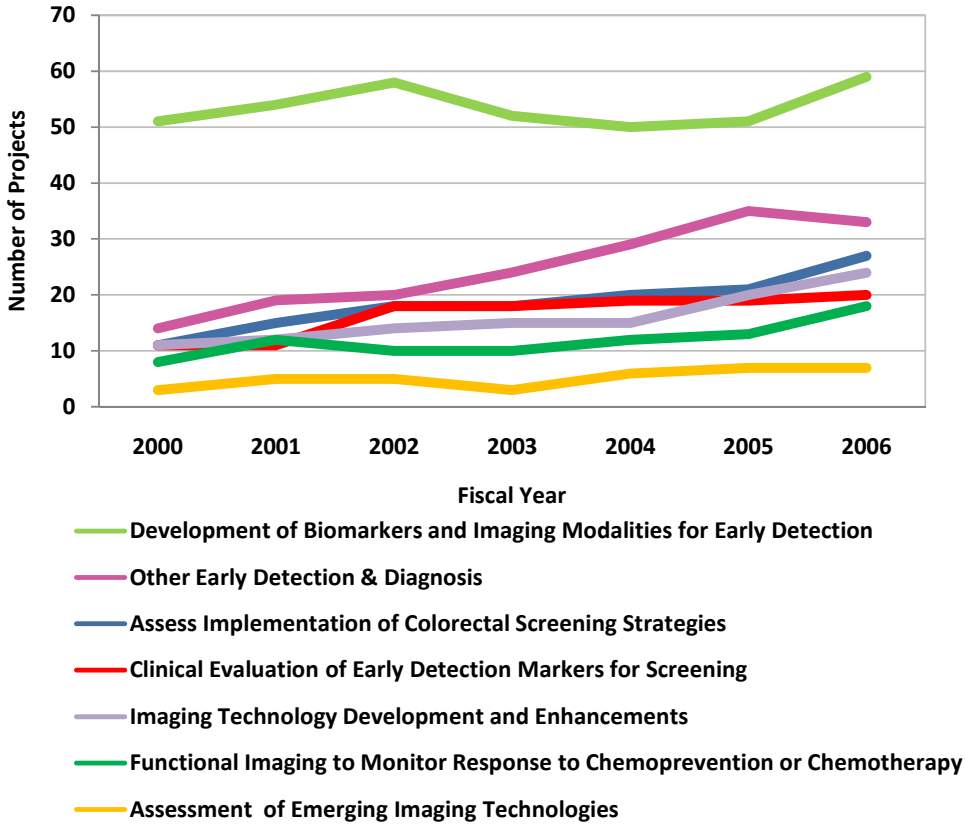

Figure 18. NCI Projects Related to Colorectal Cancer Early Detection and Diagnosis, FY2000 to FY2006

[43] For a more detailed description of these PRG research priorities, please see Table 1 and associated footnotes.

Clinical Trials

Between FY2000 and FY2006, there were 20 clinical studies related to colorectal cancer early detection and diagnosis. These include studies related to colorectal cancer diagnosis, such as detection of tumor hypoxia and sentinel lymph node biopsy studies, as well as studies related to colorectal cancer screening, including studies comparing FOBT and colonoscopy (**Figure 19**). The number of clinical trials related to diagnosis dropped in FY2002 while trials related to colorectal cancer screening increased after FY2004.

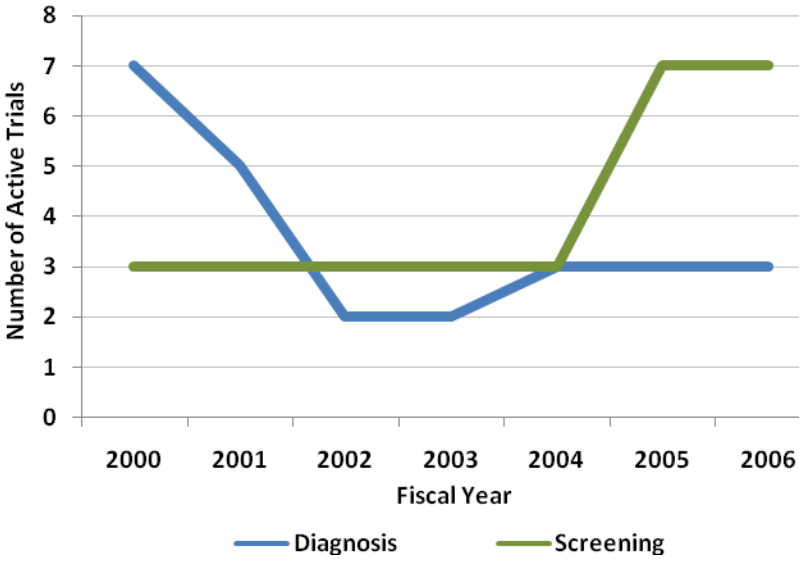

Figure 19. NCI Clinical Trials Related to Colorectal Cancer Early Detection and Diagnosis, FY2000 to FY2006

Initiatives

NCI has established the following research initiatives related to colorectal cancer early detection and diagnosis:

- The **Director's Challenge: Toward a Molecular Classification of Cancer** challenges the scientific community to harness the power of comprehensive molecular analysis technologies to redefine tumor classification, moving from morphological to molecular classification.
  - *NCI initiated the Director's Challenge program in FY1999. The program has supported four projects on the molecular classification of colon tumors, including identifying gene expression signatures of colon cancers that metastasize.*

- The **Exploratory Studies in Cancer Detection, Diagnosis, and Prognosis** promote the initial evaluation of new molecular or cellular characteristics of premalignant cells or tumors or the development of assays that will be useful for cancer detection, diagnosis, and/or prognosis.
  - *NCI has funded 12 colorectal cancer projects under this PA, including research to identify colon cancer biomarkers, the development of a new proteomic assay, and evaluation of a technique for assessing DNA in stool to screen for colorectal cancer.*

- The **Early Detection Research Network (EDRN)** brings together dozens of institutions to help accelerate the translation of biomarker information into clinical applications and to evaluate new ways of detecting cancer in its earliest stages.
  - *The EDRN currently supports eight protocols related to colon cancer, including proteomics biomarker development, screening detection of mismatch repair deficient colorectal neoplasias using stool-based DNA analysis, and proteomic profiling of serum and other body fluids for early detection of colon cancers.*

- The **Academic-Industrial Partnerships for Development and Validation of In Vivo Imaging Systems and Methods for Cancer Investigations** supports research partnerships formed by academic and industrial investigators to accelerate the translation of in vivo spectroscopic and imaging systems and methods into cancer research, clinical trials, and/or clinical practice.
  - *This program provides support for six translational research projects related to colorectal cancer. Funded studies focus on the molecular imaging of colorectal cancer cells, colonoscopy-free colon cancer screening by enhanced light, and a miniature real-time volumetric ultrasound imaging system.*

- The **In Vivo Cancer Imaging Exploratory/Developmental Grants** initiative supports research on in vivo cancer imaging for detection, diagnosis, and monitoring of response to therapy.
  - *Under this PA, NCI has funded three colorectal cancer projects, including studies of multimodality virtual endoscopy with hybrid PET/CT units, the cardiovascular effects and their impact on DCE-MRI images of three commonly used anesthetic protocols, and [18F] radiotracers that can be used to image tumors in vivo using PET scans.*

- The **Novel Technologies for In Vivo Imaging** initiative supports the development and delivery of novel in vivo image acquisition or enhancement technologies and methods for biomedical imaging and image-guided interventions and therapy.
  - *NCI has funded two colorectal cancer projects under this PA. One of them is developing new contrast agents for in vivo micro CT x-ray imaging based on nontoxic gold nanoparticles, and the other is developing advanced instrument-tracking technology to better enable image-guided cancer treatment.*

- The Tumor Glycome Laboratories of the **NIH Alliance of Glycobiologists for Detection of Cancer and Cancer Risk** discover, develop, and clinically validate cancer biomarkers based on complex carbohydrate structures attached to proteins and lipids.
  - *One project supported by this initiative is conducting quantitative deglycosylation (removal of glycans) in unfractionated biological samples from ovarian, prostate, lung, and colon cancer patients and displaying the removed glycans in quantitative glycan maps as a potential screening approach.*

- The **Application of Emerging Technologies for Cancer Research** program evaluates the usefulness of emerging molecular technologies that are ready for initial application to clinical or biological questions in cancer research.
  - *NCI is supporting five colorectal cancer projects through this RFA, including a study to develop conjugates of boronolectin-MRI contrast agents as biomarker-directed cancer imaging agents and a study of tumor-associated fibroblast activation protein.*

- The **Exfoliated Cells and Circulating DNA in Cancer Detection and Diagnosis** program supports the development of novel technologies for capturing, enriching, and preserving exfoliated abnormal cells from body fluids or effusions as well as methods for concentrating the tumor-derived subcellular material for use in biomarker studies.
  - *NCI has funded two colorectal cancer studies through this initiative. One of the funded projects is using genome amplification and analysis technologies to improve sensitivity in detecting circulating nucleic acids of tumor origin. Another project is studying the effects of therapy with new agents on putative drug targets and on downstream events.*

- The **Omnibus Solicitation of the NIH, CDC, and FDA for Small Business Innovation Research Grant Applications** initiative supports Small Business Innovation Research grants.
  - *NCI has funded seven colorectal cancer studies under this PA. One of the funded projects is developing a broadband ultrasound microsystem to image cellular structure/tissue along the gastrointestinal tract, and another project is working on a whole-mouse imaging system to fluorescently visualize tumor growth and metastasis in real time.*

Research Highlights

Recent results of NCI-sponsored research in colorectal cancer early detection and diagnosis include the following:

- *Stool Assays for Detecting Altered Human DNA*

  Stool assays of selected DNA alterations, including mutations in the APC gene, have shown high sensitivity for detecting cancer (57%–91%) and adenomas in three studies. The authors of these reports concluded that assays for altered DNA are a promising screening approach for colorectal cancer.[44,45,46]

- *New Fecal Occult Blood Test Shows Promising Results*

  Investigators tested a new type of FOBT, a fecal immunochemical test (FIT), in 5,841 participants in a large prospective study. The FIT had 82% sensitivity for detecting colorectal carcinoma and 30% sensitivity for detecting advanced colorectal adenomas; specificity was 97% for carcinomas and 97% for adenomas.[47]

- *Immunohistochemistry Versus Microsatellite Instability Testing in Phenotyping Colorectal Tumors*

  Lynch syndrome, also known as HNPCC, is characterized by early age at onset, neoplastic lesions, and MSI. MSI testing can be used when a diagnosis of Lynch syndrome is being considered. There is evidence that MSI status (stable, low, or high) may affect susceptibility to chemotherapeutic agents. Unfortunately, MSI testing is labor intensive and time consuming. In Lynch syndrome, MSI is usually attributed to mutations in the hMLH1 or hMSH2 genes. Researchers sought to determine if detection of hMLH1 and hMSH2 proteins by immunohistochemistry (IHC) in colon tumor samples could provide a surrogate approach for determining MSI status. Results showed the IHC approach to be reasonably rapid, specific, and sensitive; the absence of hMLH1 or hMSH2 predicted a high MSI status 100% of the time, and the IHC method had a sensitivity of over 92% for identifying high MSI-status tumors in the sample population.[48]

- *Revised Guidelines for Lynch Syndrome Diagnosis*

  The revised "Bethesda Guidelines" for diagnosing Lynch syndrome provide a plan for identifying which colorectal cancer patients should be screened for this inherited syndrome. The revision addressed recent advances in biochemistry and genome sequencing, including new information on the genes involved in MSI.[49] In a related study, researchers used molecular techniques to screen 1,066 colon cancer patients for Lynch syndrome mutations. Of these, 23 patients and 44 of their family members were found to harbor the telltale mutations.[50]

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[44] Ahlquist et al. *Gastroenterology.* 2000. Nov;119(5):1219–27.
[45] Dong et al. *J. Natl. Cancer Inst.* 2001. Jun 6;93(11):858–65.
[46] Traverso et al. *N. Engl. J. Med.* 2002. Jan 31;346(5):311–20.
[47] Allison et al. *J. Natl. Cancer Inst.* 2007. Oct 3;99(19):1462–70.
[48] Lindor et al. *J. Clin. Oncol.* 2002. Feb 15;20(4):1043–8.
[49] Umar et al. *J. Natl. Cancer Inst.* 2004. Feb 18;96(4):261–8.
[50] Hampel et al. *N. Engl. J. Med.* 2005. May 5;352(18):1851–60.

- *Detecting Rare DNA Sequence Defects*

  A modified version of an assay developed to quantify mutant DNA fragments in the circulation of cancer patients showed that the plasma of patients with advanced colorectal cancer consistently contained mutant APC DNA. The investigators also found mutant APC DNA molecules in more than 60% of patients with early-stage colorectal cancers.[51]

- *Flexible Sigmoidoscopy Results*

  An analysis of data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial showed that 83% of participants who were offered sigmoidoscopy agreed to the procedure, which is a high rate of acceptance. Of those who underwent flexible sigmoidoscopy, 23% of participants ages 55–74 had at least one polyp or mass in their lower colon. The PLCO Trial will eventually show whether screening reduces the death rate from the four cancers being studied.[52]

[51] Diehl et al. *Proc. Natl. Acad. Sci. USA*, 2005. Nov 8;102(45):16368–73.
[52] Weissfeld et al. *J. Natl. Cancer Inst.* 2005. Jul 6;97(13):989–97.

Treatment and Prognosis

Research Projects

The Colorectal Cancer PRG members identified the following research priorities to improve the understanding of colorectal cancer treatment and prognosis:[53]

- Discover markers of prognosis and treatment response.
- Identify surrogate markers of drug response that help define drug mechanism of action and predict clinical efficacy.
- Identify and validate gene-based drug targets.
- Foster partnerships to improve patient access and facilitate conduct of clinical trials.
- Enhance local and regional therapy for colorectal cancer by fostering uniform delivery of accepted treatments and development of novel treatment regimens.
- Develop and validate markers of biological activity to facilitate clinical trials and to develop novel therapeutics.

Between FY2000 and FY2006, there were 408 unique NCI-funded projects that addressed colorectal cancer treatment and prognosis. A significant portion of these projects relate directly to the PRG priorities, and most of these address the discovery of prognostic markers and treatment response (**Figure 20**). Studies addressing the discovery or development of systemic treatment approaches (e.g., vaccines, immunotherapy, radioimmunotherapy, or chemotherapy) make up a large proportion of the research during these years as well. These projects are not addressed in any of the specific PRG priorities but are included in the category called "Other Treatment & Prognosis."

[53] For a more detailed description of these PRG research priorities, please see Table 1 and associated footnotes.

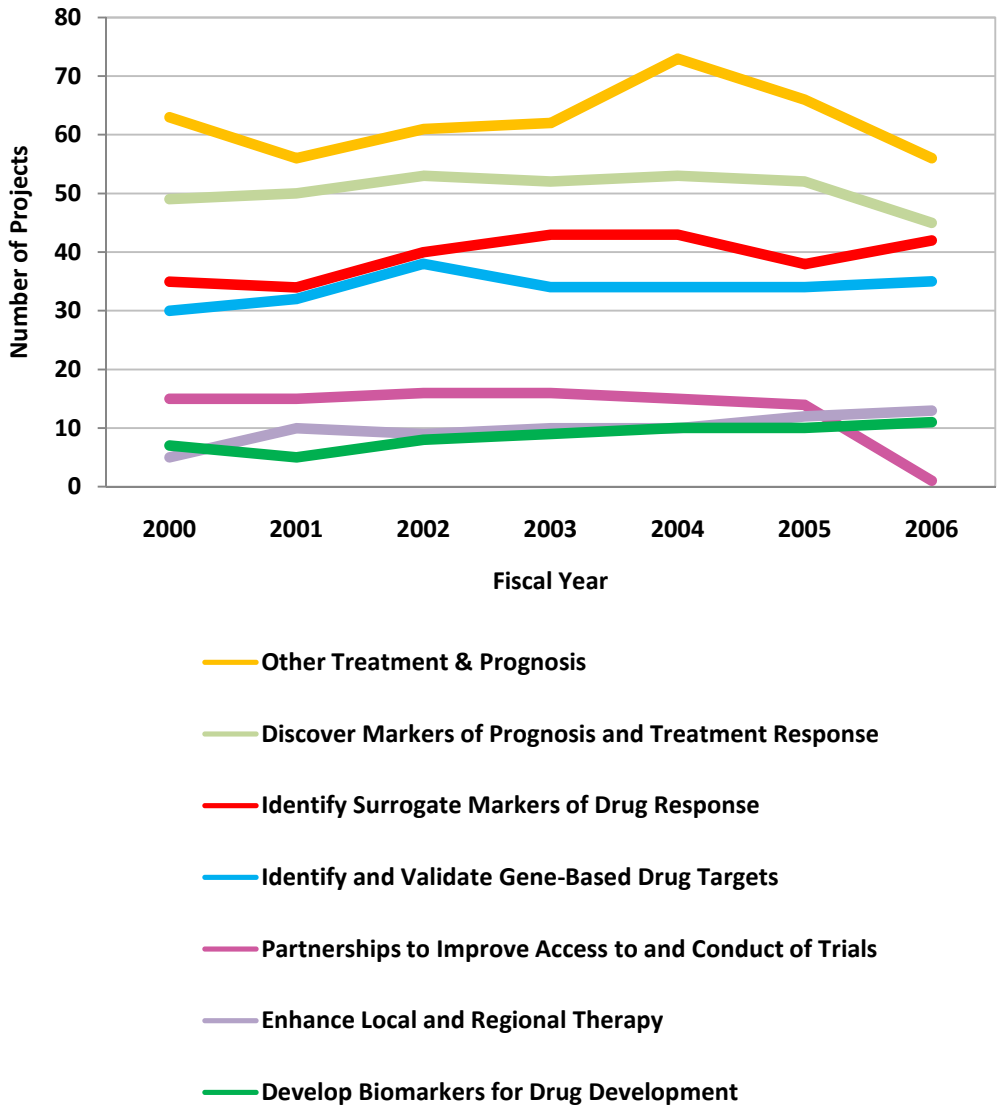

Figure 20. NCI Projects Related to Colorectal Cancer Treatment and Prognosis, FY2000 to FY2006

Clinical Trials

Between FY2000 and FY2006, there were a total of 249 clinical studies that addressed colorectal cancer treatment and prognosis. These studies included standard phased therapeutic trials of novel chemotherapies, immunotherapies, targeted therapies, or radiotherapies (or combinations of these), as well as clinical studies that use molecular techniques to measure biomarkers of treatment response (**Figure 21**). While the number of therapeutic clinical trials in colorectal cancer has declined since FY2000, there has been an increase in the number of biomarker studies during these years.

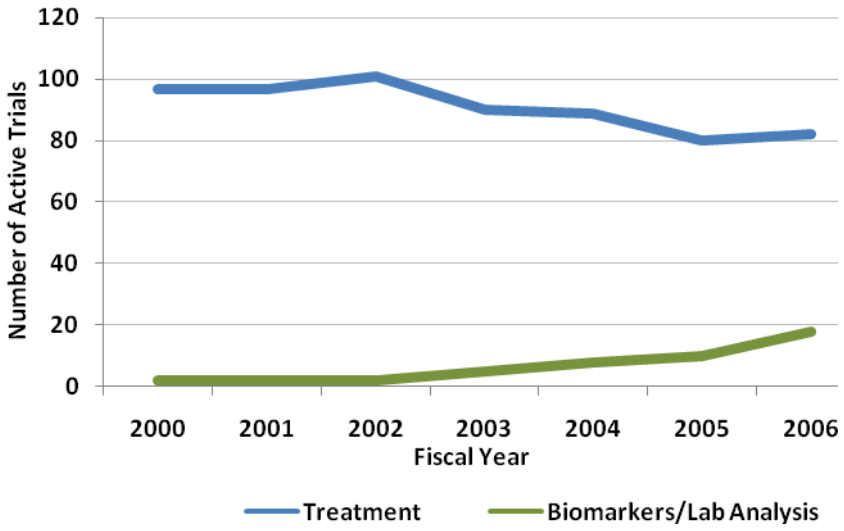

Figure 21. NCI Clinical Trials Related to Colorectal Cancer Treatment and Prognosis, FY2000 to FY2006

Initiatives

NCI has established the following research initiatives related to colorectal cancer treatment, prognosis, and prediction:

- The **Correlative Studies with Specimens from Multi-Site Trials** program fosters collaborations and interactions between basic researchers, scientists working in private industry, and clinical investigators to perform clinical translational research on promising predictive and prognostic markers.
  - *NCI has funded three colorectal cancer studies under this PA, including research focused on the molecular actions of imatinib mesylate in gastrointestinal stromal tumors (GISTs), the development and evaluation of pharmacogenetics for advanced colorectal cancer, and the molecular characteristics of primary GIST as predictors of clinical outcome after adjuvant therapy.*

- The **Quick-Trials for Novel Cancer Therapies: Exploratory Grants** initiative supports translational research on new agent development to ensure the timely exploitation of new cancer therapeutic approaches.
  - *NCI has funded 10 colorectal cancer projects under this PAR, including studies to reduce drug resistance by arsenic trioxide, evaluation of a multi-epitope vaccine for lung and colorectal cancer, and evaluation of the effectiveness of irinotecan in combination with celecoxib for colorectal cancer.*

- The **Molecular Targets for Cancer Drug Discovery: Exploratory Agents** program promotes full use of the cancer biology knowledge base for cancer-relevant target validation and drug discovery for treatment and prevention.
  - *Eleven colorectal cancer projects were funded under this initiative, including research to validate dUTPase as a target for drug discovery and a study to validate de novo DNA cytosine-C5 methyltransferases as appropriate molecular targets for anti-cancer drug development.*

- The **Clinical Cancer Therapy and Prevention Research** program supports translational, clinical, therapeutic, and preventive studies and trials of neoplastic diseases in humans and encourages clinical researchers to collaborate with basic scientists to translate insights in cancer genetics, cancer epigenetics, and cancer biology, coupled with the development of new anti-cancer agents, into innovative cancer intervention studies and trials.
  - *NCI has funded three colorectal cancer studies under this PA, including research to elucidate the prognostic significance of genes that influence sensitivity to the 5-FU and leucovorin chemotherapy regimen, studies that assess the molecular and physiological consequences of bevacizumab treatment, and developmental research on dendritic cell immunotherapies for colorectal cancer.*

- The **Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses (FLAIR)** provides small businesses with the opportunity to develop new treatments for rare cancers that are often overlooked because of small market considerations.
  - *This program has provided support for three drug discovery efforts related to colorectal cancer, including research on novel polymeric prodrugs of camptothecin, a preventive agent for colorectal cancer that inhibits several signaling pathways responsible for colon carcinogenesis, and novel inhibitors of human palmitoyl acyltransferases as cancer therapeutic agents.*

- The **Developmental Projects in Complementary Approaches to Cancer Care** program encourages and supports the development of basic and clinical complementary cancer research that will provide the basis for more extended research projects by establishing the methodological feasibility, strengthening the scientific rationale for these projects, and collecting preliminary data.
    - *NCI has funded four colorectal cancer projects through this initiative, including studies of cancer prevention by West African medicinal plants, acupuncture to help patients recover from colectomy, and the anti-cancer effects of green tea catechins.*

Research Highlights

Recent results of NCI-sponsored research in colorectal cancer treatment and prognosis include:[54]

- *New Drug Regimen Shows Clear Benefit for Treating Advanced Colorectal Cancer*
  Initial results from a large, randomized clinical trial for patients with metastatic colorectal cancer show that those who received the experimental FOLFOX4 drug regimen (5-FU/leucovorin/oxaliplatin) lived months longer than those who received standard therapy. Patients also had a longer time before their tumors progressed, a better response rate, and fewer severe side effects.[55] FOLFOX4 also demonstrated superior clinical efficacy in patients with advanced colorectal cancer when compared to fluorouracil plus leucovorin alone or fluorouracil plus oxaliplatin alone.[56]

- *Adding Bevacizumab (Avastin®) Improves Outcomes in Advanced Colorectal Cancer*
  Bevacizumab, an antiangiogenic agent, inhibits tumor growth by blocking the formation of new blood vessels. This drug, combined with chemotherapy, has been shown to improve survival for previously untreated patients with metastatic colorectal cancer. In the current study, researchers tested whether bevacizumab (at 10 mg/kg) can improve survival duration in patients with previously treated metastatic colorectal cancer. Results show that the addition of bevacizumab to oxaliplatin, fluorouracil, and leucovorin improves survival duration for patients with previously treated metastatic colorectal cancer.[57] In a separate study, researchers demonstrated a significant increase in overall survival as well as progression-free survival for patients who received bevacizumab in addition to a standard chemotherapy regimen consisting of irinotecan, fluorouracil, and leucovorin.[58]

- *Laparoscopic Surgery a Good Alternative for Some Colon Cancer Patients*
  Laparoscopic colectomy refers to a surgical technique performed with the aid of a laparoscope to remove all or part of the colon through several small incisions made in the wall of the abdomen. Researchers compared recovery time and rates of cancer recurrence in colorectal cancer patients who had their tumors removed laparoscopically to those who underwent traditional open colectomy. The study revealed that rates of cancer recurrence were not significantly different in the two groups and that patients who underwent laparoscopic colectomy recovered more quickly than those who had the traditional surgery.[59,60]

[54] While not all of the clinical trials featured in the "Research Highlights" section are fully funded by the NCI, the resulting publications summarized here do cite NCI support.
[55] Goldberg et al. *J. Clin. Oncol.* 2004. Jan 1;22(1):23–30.
[56] Rothenberg et al. *J. Clin. Oncol.* 2003. Jun 1;21(11):2059–69.
[57] Giantonio et al. *J. Clin. Oncol.* 2007. Apr 20;25(12):1539–44.
[58] Hurwitz et al. *N. Engl. J. Med.* 2004. Jun 3;350(23):2335–42.
[59] Weeks et al. *JAMA* 287 (3): 321–8, 2002.
[60] *N. Engl. J. Med.* 2004. May 13;350(20):2050–9.

- *U.S. Food and Drug Administration (FDA) Approves Panitumumab for Metastatic Colon Cancer*

  Panitumumab (Vectibix™) is a monoclonal antibody that interferes with cell growth signals by binding to the EGFR on some cancer cells. Researchers recently evaluated panitumumab in a randomized, controlled clinical trial in colorectal cancer patients who had been treated with the drugs fluoropyrimidine, oxaliplatin, and irinotecan. The results showed a benefit for patients treated with panitumumab in progression-free survival but not in overall survival. Panitumumab has been approved by the FDA for the treatment of metastatic colorectal cancer that has progressed despite standard chemotherapy.[61]

- *Gene Polymorphism Determines Response to Chemotherapy*

  The thymidylate synthase (TS) enzyme is involved in DNA synthesis and is inhibited by certain chemotherapy agents such as 5-FU. Researchers tested whether polymorphisms in the TS gene could predict clinical outcome in colorectal cancer patients treated with 5-FU. The study revealed that variations in the TS gene were correlated with significant differences in the degree of treatment response and toxicity following 5-FU treatment. These findings suggest that genotyping for the TS polymorphism may help identify patients who are more likely to respond to 5-FU-based chemotherapy.[62]

- *Colorectal Tumors Responding to 5-FU Have Low Gene Expression Levels of Dihydropyrimidine Dehydrogenase*

  Studies have shown that differences in the expression levels of certain genes can affect response to chemotherapy. For example, the enzyme dihydropyrimidine dehydrogenase (DPD) is responsible for the catabolism and clearance of the chemotherapy drug 5-FU. In the current study, researchers investigated the association between intratumoral gene expression of DPD and the response of colorectal tumors to 5-FU. The study found that high levels of DPD were correlated with a poor response to 5-FU.[63]

[61] Giusti et al. *Oncologist.* 2007. May;12(5):577–83.
[62] Pullarkat et al. *Pharmacogenomics J.* 2001;1(1):65–70.
[63] Salonga et al. *Clin. Cancer Res.* 2000. Apr;6(4):1322–7.

Cancer Control, Survivorship, and Outcomes

Research Projects

The Colorectal Cancer PRG members identified the following research priorities to improve the understanding of colorectal cancer control, survivorship, and outcomes:[64]

- Develop conceptual models/methods that relate to the effectiveness, efficacy, and cost-effectiveness of intervention strategies.
- Characterize patterns of prevention, screening, treatment, and quality of care.
- Assess the effectiveness of screening, prevention, and treatment in special populations.
- Improve health system-oriented access to screening and treatment.
- Improve patient-oriented access to screening and treatment.
- Evaluate post-treatment care and subsequent outcomes.
- Study the effect of psychosocial distress on diagnostic and therapeutic compliance and outcomes.
- Assess the outcomes of genetic screening.

Between FY2000 and FY2006, there were 264 unique NCI-funded projects that addressed colorectal cancer control, survivorship, or outcomes. The annual number of NCI projects related to colorectal cancer control, survivorship, and outcomes increased from 75 to 141 in this time frame (**Figure 22**). Most of the projects relevant to this category focused on the PRG research priority that addressed the development of conceptual models or methods that relate to the efficacy, effectiveness, and cost-effectiveness of intervention strategies, including prevention, diagnostic evaluation, treatment modalities, and strategies to enhance quality of care.

[64] For a more detailed description of these PRG recommendations, please see Table 1 and associated footnotes.

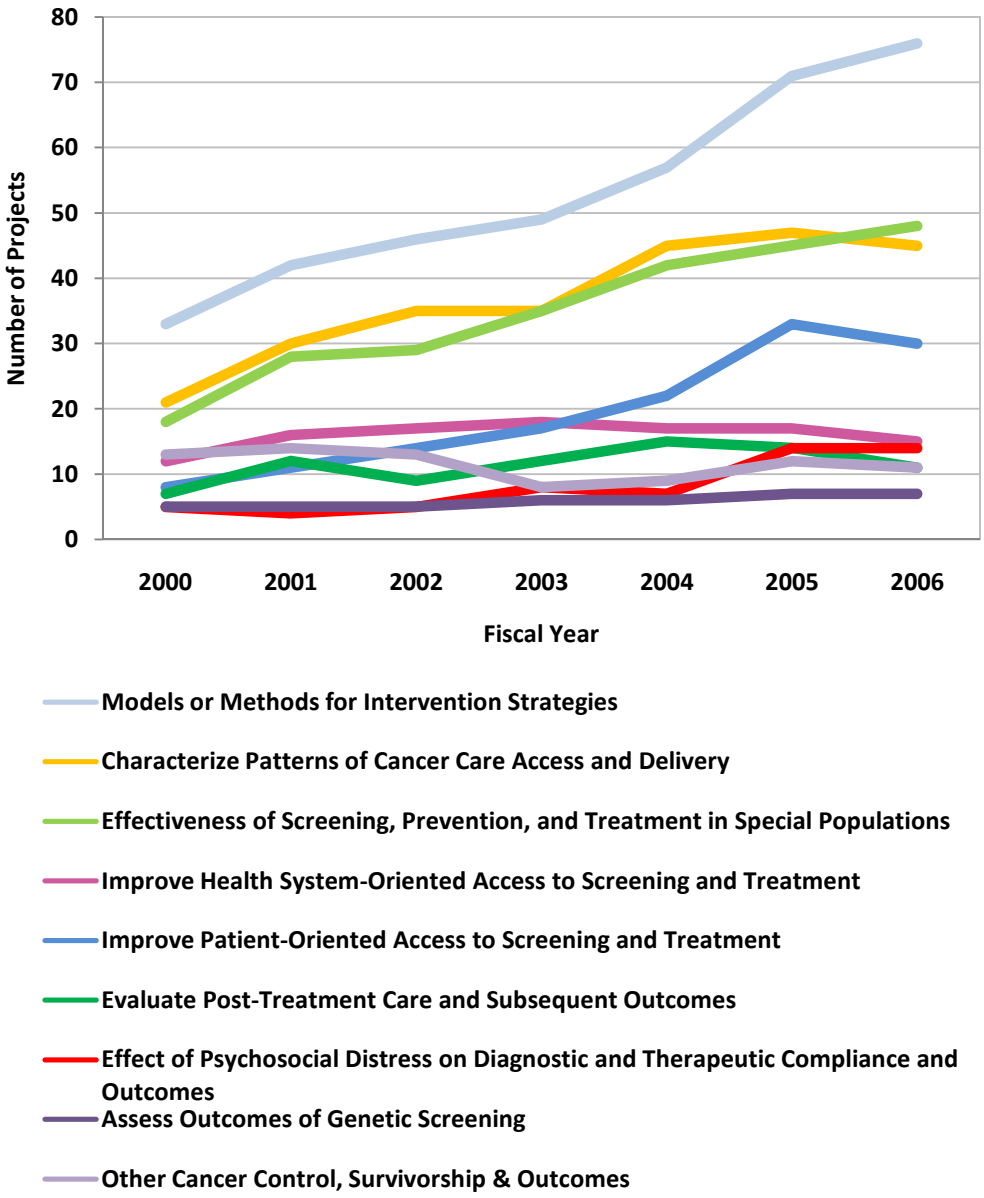

Figure 22. NCI Projects Related to Colorectal Cancer Control, Survivorship, and Outcomes, FY2000 to FY2006

Clinical Trials

Between FY2000 and FY2006, NCI sponsored 41 clinical trials related to colorectal cancer control, survivorship, and outcomes. These trials include studies that explore supportive care options for colorectal cancer patients, behavioral studies to measure exercise or screening compliance, health services research studies, education and counseling studies to increase screening or for those undergoing genetic testing, and methods development studies (**Figure 23**).

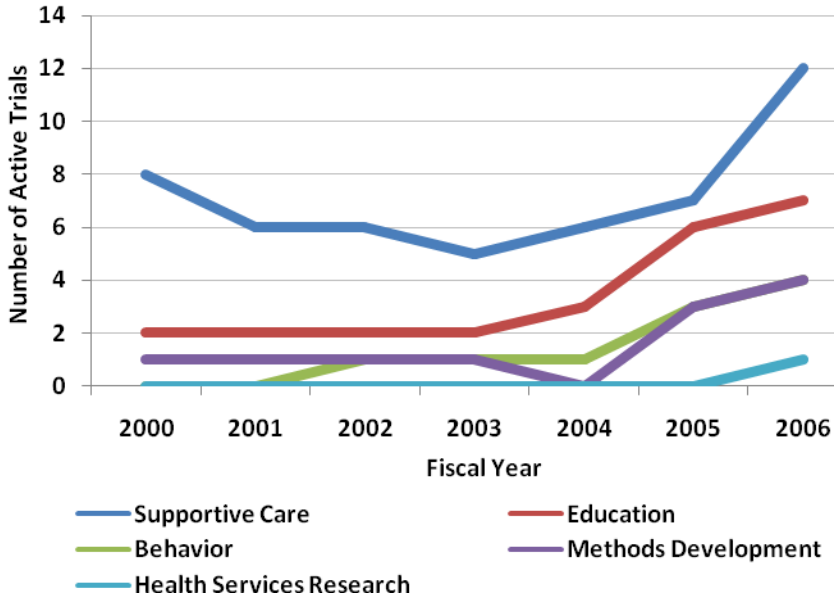

Figure 23. NCI Clinical Trials Related to Colorectal Cancer Control, Survivorship, and Outcomes, FY2000 to FY2006

Initiatives

NCI issued the following research initiatives related to colorectal cancer control, survivorship, and outcomes:

- The **Colorectal Cancer Screening in Primary Care Practice** program encourages health services, social and behavioral, and outcomes researchers to develop innovative research projects to increase the knowledge base for enhanced translation of effective colorectal cancer screening techniques into community practice.
  - *NCI has supported 17 colorectal cancer projects through this PAR, including studies to increase colon cancer screening rates, especially among underserved populations, and to identify barriers to colorectal cancer screening.*

- The **Small Grants for Behavioral Research in Cancer Control** initiative supports pilot or feasibility studies, development and testing of new methodologies, development and testing of new research technology, secondary analysis of existing data, self-contained research projects, or innovative studies that provide a basis for more extended research.
  - *Ten colorectal cancer projects have been funded through this program, including studies on physical activity in urban African Americans, screening barriers in American Indians/Alaska Natives, and factors associated with stage at diagnosis of colorectal cancer in an underserved population.*

- The **Exploratory Grants for Behavioral Research in Cancer Control** program supports the use of developmental and exploratory approaches to primary and secondary cancer prevention and control.
  - *This program has provided support for nine colorectal cancer projects on topics such as decision making about cancer screening among older women, an expressive writing intervention to assist in adjustment to colorectal cancer, and colorectal cancer beliefs of African American males.*

- The **Cancer Intervention and Surveillance Modeling Network (CISNET)** is a consortium of NCI-sponsored investigators who use modeling to improve the understanding of the impact of cancer control interventions on population trends in incidence and mortality.
  - *CISNET was initially established in FY2000. It has supported five colorectal cancer projects, including a population-based model for colorectal cancer, a genetic screening policy model for colorectal cancer, and a cost-effectiveness model of the National Colonography Trial. A new web-based tool provides computer simulations of colorectal disease progression and is designed to inform cancer control planning and public policy decision making about reducing colorectal cancer mortality.*

- The **Cancer Surveillance Using Health Claims-Based Data** program supports research involving the use of health claims data for cancer surveillance.
  - *Through this program, NCI has provided support for four colorectal cancer projects, including studies of racial disparities in cancer outcomes, the medical care burden of cancer, and the receipt of colorectal cancer screening.*

- The **Cancer Care Outcomes Research and Surveillance Consortium** supports prospective studies in cohorts of newly diagnosed lung and colorectal cancer patients on medical care practices used to manage patients over the course of their disease, various outcomes associated with these practices, and information about patient and provider behaviors and perceptions.
    - *NCI has supported three colorectal cancer studies under this RFA. Funded research is focused on the development of methods for defining, measuring, and reporting on the quality of cancer care; establishing a system to examine the relationship of processes of care to clinical and patient care outcomes; and understanding the relationship between cancer care and patient-centered outcomes.*

- The **Cancer Research Network** consists of the research programs, enrolled populations, and data systems of 12 health maintenance organizations nationwide. The network conducts research on cancer prevention, early detection, treatment, long-term care, and surveillance.
    - *The network currently funds five colorectal cancer research projects, including studies of the impact of hormone replacement therapy and NSAIDs on risk of recurrence and short-term survival, the accuracy of automated data for colorectal cancer screening, and studies to understand age-specific differences in cancer of the cecal colon.*

Research Highlights

Recent results of NCI-sponsored research in cancer control, survivorship, and outcomes include:

- *Relationship Between Colorectal Cancer Risk and Smoking, Drinking, and Gender*
  A retrospective analysis of self-reported data from 166,172 patients with colorectal cancer in a health maintenance organization database found that the risk of developing advanced colorectal cancer at a younger age is higher in males and in people who smoke or drink. Although recommendations generally call for colorectal cancer screening to begin at age 50, this analysis suggests that people who smoke or drink might benefit from screening at an earlier age.[65]

- *Exercise Can Reduce Risk of Colorectal Cancer Recurrence*
  Two prospective, observational studies found that patients who participated in regular physical activity after being diagnosed with early-to-later stage colorectal cancer reduced their likelihood of cancer recurrence and mortality by 40%–50% or more compared to patients who participated in little or no physical activity.[66, 67]

- *Colonoscopy Versus Sigmoidoscopy in Women*
  A study of 1,463 asymptomatic women ages 50–79 at average risk of colorectal cancer found that flexible sigmoidoscopy alone would not have found almost two-thirds of the advanced polyps in these women. These findings could signify that colonoscopy should be the standard screening test in this population.[68]

- *Colon Cancer Disparities*
  A study found that 70% of white patients received adjuvant chemotherapy after surgery for stage III colon cancer, compared to just 59% of black patients. In another study of 1,067 colorectal cancer patients, patients who were not white or did not speak English reported many more problems with their cancer care than white patients and those who speak English.[69,70]

- *Colorectal Cancer Screening Guidelines Not Being Followed*
  An analysis of data from surveys of physicians and patients found that many clinicians are not screening their patients routinely for colorectal cancer using the home-based FOBT as recommended by the U.S. Preventive Services Task Force. Only 26.3% of physicians in the survey used the FOBT home test exclusively, as recommended by the task force.[71]

- *Fecal Occult Blood Screening and Colorectal Cancer Incidence*
  When researchers followed 46,551 participants (most were ages 50–80) in the Minnesota Colon Cancer Control Study for 18 years, they found that patients who received an FOBT either every year or every other year were less likely to develop colorectal cancer than those who were not screened.[72]

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[65] Zisman et al. *Arch. Intern. Med.* 2006. Mar 27;166(6):629–34.
[66] Meyerhardt et al. *J. Clin. Oncol.* 2006. Aug 1;24(22):3535–41.
[67] Meyerhardt et al. *J. Clin. Oncol.* 2006. Aug 1;24(22):3527–34.
[68] Schoenfeld et al. *N. Engl. J. Med.* 2005. May 19;352(20):2061–8.
[69] Baldwin et al. *J. Natl. Cancer Inst.* 2005. 97(16):1211–1220.
[70] Ayanian et al. *J. Clin. Oncol.* 2005. Sep 20;23(27):6576–86.
[71] Nadel et al. *Ann. Intern. Med.* 2005. Jan 18;142(2):86–94.
[72] Mandel et al. *N. Engl. J. Med.* 2000. Nov 30;343(22):1603–7.

- *Recommended Surgical Procedure Might Be Underused*

  Researchers used NCI's SEER (Surveillance, Epidemiology, and End Results) registry to review the care and outcomes of 8,400 patients who had surgery to remove colon or rectal tumors that had grown into nearby organs. Two-thirds of patients had only the tumor removed, and only one-third of patients had the tumor and adjacent organs removed (multivisceral resection). However, those who had a multivisceral resection had much higher 5-year survival rates.[73]

- *Difficulty of Increasing Colorectal Cancer Screening Rates*

  A randomized, controlled trial attempted to increase the rate of colorectal cancer screening by providing start-up materials and support to encourage colorectal cancer screening in a managed care organization's patients. Over the study's 2.2 years, only 29% of eligible patients in the intervention group had received the recommended screening procedures, and the screening rates did not differ significantly between the intervention and control groups.[74]

- *Americans Unclear on When to Get Cancer Screening Tests*

  The Health Information National Trends Survey (HINTS), a nationally representative telephone survey of the general population, found that 40% of respondents could not name an available screening test for colorectal cancer. However, 54% knew that colorectal cancer screening is recommended for men and women ages 50 and older.[75]

- *Selenium and Colorectal Cancer Risk*

  Researchers found that people with a higher blood selenium concentration had a lower risk of developing recurrent colorectal adenomas. This study pooled data from three separate randomized trials that tested the effects of different nutritional interventions on colorectal adenoma prevention to increase the precision of its risk estimates. [76]

- *Cost-Effectiveness of Colorectal Cancer Screening*

  An assessment of the consequences, costs, and cost-effectiveness of colorectal cancer screening on people at average risk of the disease found that screening significantly reduces mortality, and its costs are similar to those of other cancer screening procedures.[77]

- *Physicians May Conduct Unnecessary Surveillance Colonoscopies*

  Physicians are apparently conducting surveillance colonoscopies more frequently than evidence-based guidelines recommend. This overuse of colonoscopy could reduce quality of care because this procedure is associated with inconvenience to patients and the possibility of complications. Overuse can also cause reduced access and longer waiting periods for people at higher risk of colorectal cancer.[78]

[73] Govindarajan et al. *J. Natl. Cancer Inst.* 2006. Oct 18;98(20):1474–81.
[74] Ganz et al. *Cancer.* 2005. Nov 15;104(10):2072–83.
[75] Health Information National Trends Survey. *Hintsbriefs* August 2006;3:1.
[76] Jacobs et al. *J. Natl. Cancer Inst.* 2004. 96(22):1669–1675.
[77] Frazier et al. *JAMA.* 2000. Oct 18;284(15):1954–61.
[78] Mysliwiec et al. *Ann. Intern. Med.* 2004. Aug 17;141(4):264–71.