National Cancer Institute

Pancreatic Cancer: Six Years of Research Progress

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

Pancreatic Cancer: Six Years of Research Progress

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Highlights of NCI's Recent Progress in Pancreatic Cancer

Why NCI Performed This Analysis

Background

In 2000, the National Cancer Institute (NCI) convened a multidisciplinary committee of scientists, clinicians, and advocates—the Pancreatic Cancer Progress Review Group (PRG)—to review the pancreatic cancer research field and make recommendations concerning the most urgent needs and promising directions for future NCI investment. The PRG's report, *Pancreatic Cancer: An Agenda for Action,* was issued in February 2001 and provided priority recommendations in six major areas:

- Health of the Field and Overarching Issues
- Tumor Biology
- Risk, Prevention, Screening, and Diagnosis
- Therapy
- Health Services Research
- Scientific Toolkit

NCI conducted an analysis, summarized in this report, to assess progress over the past 6 years in each of these areas.

Approach

A retrospective analysis performed in 2007 addressed measures of progress such as trends in numbers of NCI-funded pancreatic cancer research projects, publications, initiatives, and clinical trials.

Results

During the past 6 years, NCI funding for pancreatic cancer increased by 240%. The number of pancreatic cancer research projects grew substantially in all of the PRG priority areas except health services research, possibly because of the very limited survival duration of individuals with this disease. In the coming years, NCI will continue to strive to ensure that research results are translated into practice to make a difference for those affected by pancreatic cancer.

What NCI Found

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

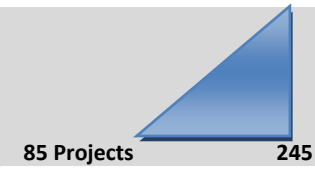
- Since the 2001 Pancreatic Cancer PRG report was published, NCI's investment in pancreatic cancer grew by 240%, from $21.8 million to $74.2 million. In comparison, the total NCI budget increased by 26% during this period.
- The number of investigators with NCI-funded R01 grants increased by 171% between FY2000 and FY2006.

Fiscal Year	NCI Investment for Pancreatic Cancer ($M)	% Increase from Previous Year (cumulative % increase since 2001 PRG report)	Total NCI Budget ($M)	% Increase from Previous Year (cumulative % increase since 2001 PRG report)
2000	20.0	16% (N/A)	3,311	15% (N/A)
2001[a]	21.8	9% (N/A)	3,754	14% (N/A)
2002	33.1	51% (51%)	4,177	11% (11%)
2003	42.3	28% (94%)	4,592	10% (22%)
2004	52.7	25% (141%)	4,724	3% (26%)
2005	66.7	27% (206%)	4,795	2% (28%)
2006	74.2	11% (240%)	4,747	-1% (26%)

[a] The PRG report was published in February 2001.

Progress was also made in the following overarching areas:

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



↑ 188%

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

↑ 171%

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

↑ 107%

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

Additional NCI Activities to Advance Pancreatic Cancer Research Include:

Exception Funding

Since the 2001 PRG, NCI funded 19 pancreatic cancer research projects (out of 24 eligible applications) through targeted exception funding efforts. These projects address three of the PRG priority areas: tumor biology; risk, prevention, screening, and diagnosis; and therapy.

Clinical Trials

Between FY2000 and FY2006, NCI sponsored 160 clinical trials relevant to pancreatic cancer. The majority of these were treatment trials and most were either Phase I or Phase II trials.

Specialized Programs of Research Excellence

NCI currently supports one specialized and two exploratory SPOREs and two gastrointestinal cancer SPOREs with pancreatic cancer components.

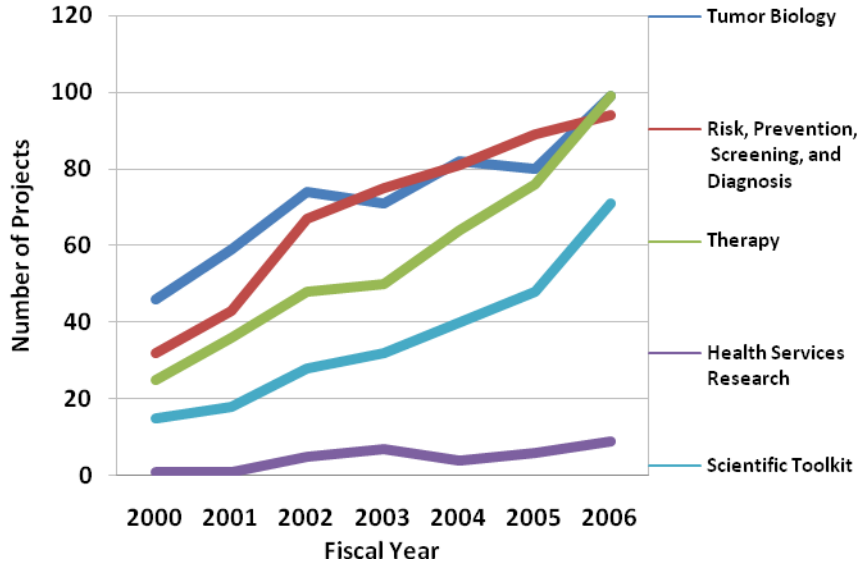
NCI-Funded Institutions

Currently, 84 U.S. research institutions and 5 overseas institutions receive NCI funding for pancreatic cancer research.

Pancreatic Cancer Research Map

In collaboration with the Pancreatic Cancer Action Network (PanCAN) and the Lustgarten Foundation for Pancreatic Cancer Research, NCI created the Pancreatic Cancer Research Map (http://www.cancermap.org/pancreatic/index.jsp), a web-based tool for tracking pancreatic cancer research, clinical trials, and investigators.

Research Projects Addressing Priority Areas Defined by the Pancreatic Cancer PRG[a] Increased between FY2000 and FY2006:



[a] The recommendations in the PRG priority area "Health of the Field and Overarching Issues" are overarching and do not correspond to specific research projects supported by NCI. Progress in achieving these recommendations is addressed on the first page of this summary.

Research Highlights:

Tumor Biology:

- Overexpression of the cyclin D1 protein can contribute to drug resistance of pancreatic cancer cells.
- Promising targets for modulating growth, blood vessel formation, and metastasis in pancreatic cancer have been identified.

Risk, Prevention, Screening, and Diagnosis:

- Researchers have developed a novel nanoparticle-based imaging agent that can help pinpoint pancreatic ductal adenocarcinoma.
- Increased cigarette smoking, diabetes mellitus, and bronchial asthma; high intake of saturated fat; and exposure to higher insulin concentrations and insulin resistance are associated with increased risk of pancreatic cancer in male smokers.

Therapy:

- Patients with advanced pancreatic cancer treated with the drug erlotinib in addition to gemcitabine had modest improvement in 1-year survival rates.
- Genetic variations in drug metabolism, DNA damage response, and DNA repair affect clinical response to pancreatic cancer therapy and patient survival.

Scientific Toolkit:

- A new pancreatic cancer-specific BRCA2-deficient mouse model will be used to test novel therapies for treating pancreatic cancer resulting from genetic defects.
- An in vitro model will be used to determine if restoration of signaling of the tumor-suppressor gene *Smad4* creates a cell that is more sensitive to treatment.

THE PANCREATIC CANCER BURDEN

Although pancreatic cancer accounts for only 2% of all new cancers in the United States, it is the fourth leading cause of cancer death among males and females. In 2007[1], an estimated 37,130 individuals will be diagnosed with pancreatic cancer and an estimated 33,370 deaths will occur as a result of this disease. The total number of pancreatic cancer cases and deaths has increased since 2003 (**Figure 1**).

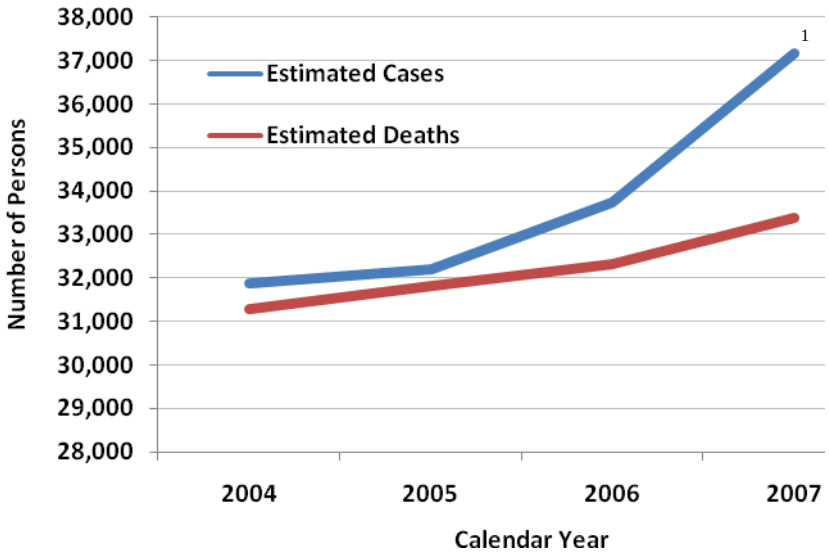


Figure 1. Estimated New Cases and Deaths for Pancreatic Cancer by Year, 2004–2007
Source: American Cancer Society: Cancer Facts and Figures 2004–2007
Available at: ***http://www.cancer.org/docroot/home/index.asp***

Overall pancreatic cancer incidence rates have not changed dramatically over the past 20 years (**Figure 2**). Rates have declined slightly for some racial and ethnic populations, including blacks, who exhibit a much higher incidence rate than whites, Hispanics, Asians/Pacific Islanders, and American Indians/Alaska Natives. The fluctuation observed in pancreatic cancer incidence rates for American Indians/Alaska Natives is most likely due to low sample numbers in this population. 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 (see: *CA Cancer J Clin. 2007 Jan-Feb;57(1):30-42*). The new method predicts an 8.9% higher number of estimated cases compared to the old method that was used for years prior to 2007.

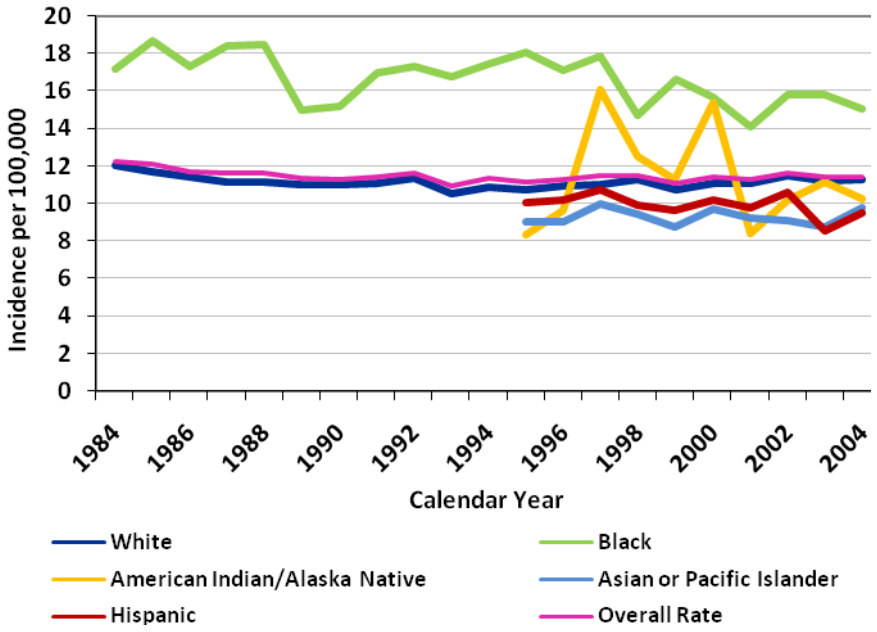


Figure 2. Incidence Rate Trends for Pancreatic Cancer by Racial/Ethnic Group, 1984–2004
Source: NCI's Surveillance, Epidemiology, and End Results (SEER) Program

As shown in **Figure 3**, pancreatic cancer incidence rates are higher for black males than for black females, and rates are higher for white males than for white females. The cause(s) of this gender disparity is not yet understood.

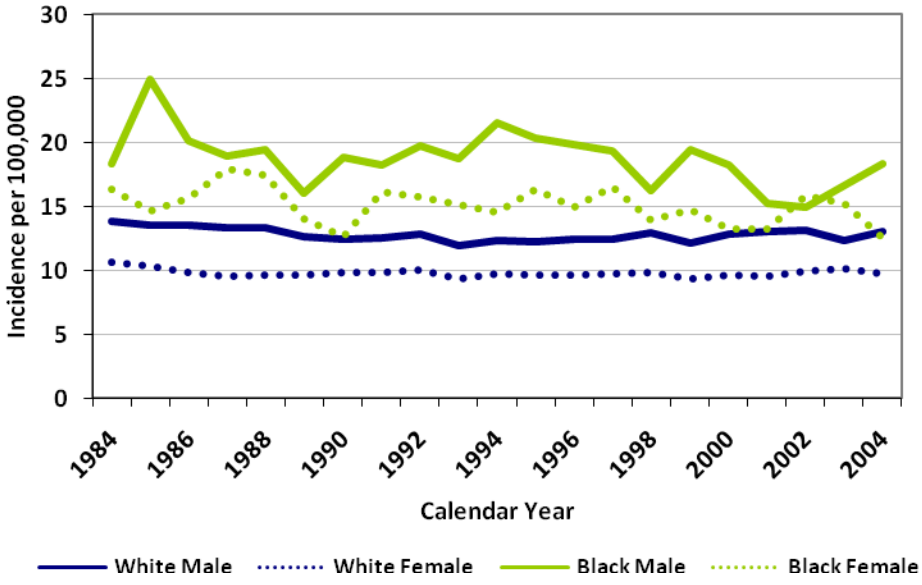


Figure 3. Male–Female Incidence Rate Trends for Pancreatic Cancer, 1984–2004
Source: NCI's SEER Program

Overall mortality rates for pancreatic cancer have been relatively stable over the past 20 years for which data are available (**Figure 4**). As shown in **Figure 5**, pancreatic cancer mortality rates are higher for black males than for black females, and rates are higher for white males than for white females. Pancreatic cancer survival is poor compared to nearly all other types of cancer—only about 4% of diagnosed patients live more than 5 years. Delayed diagnosis is a major cause of poor survival; pancreatic cancer is difficult to detect in its early stages and seldom is diagnosed before it has spread extensively. Note that mortality rates are only available for Hispanics, Asians/Pacific Islanders, and American Indians/Alaska Natives from 1995 onward.

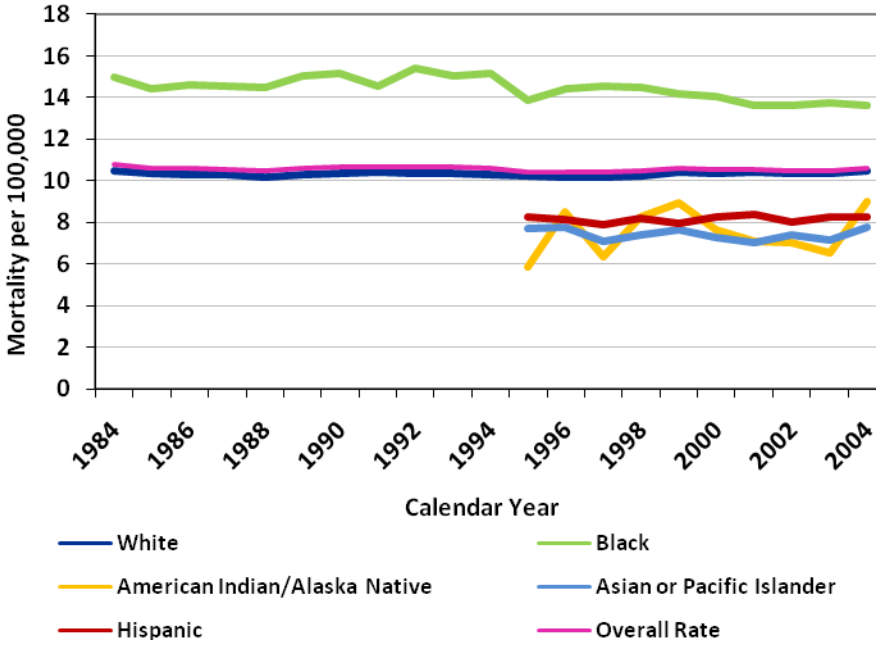


Figure 4. Mortality Rate Trends for Pancreatic Cancer, 1984–2004
Source: NCI's SEER Program

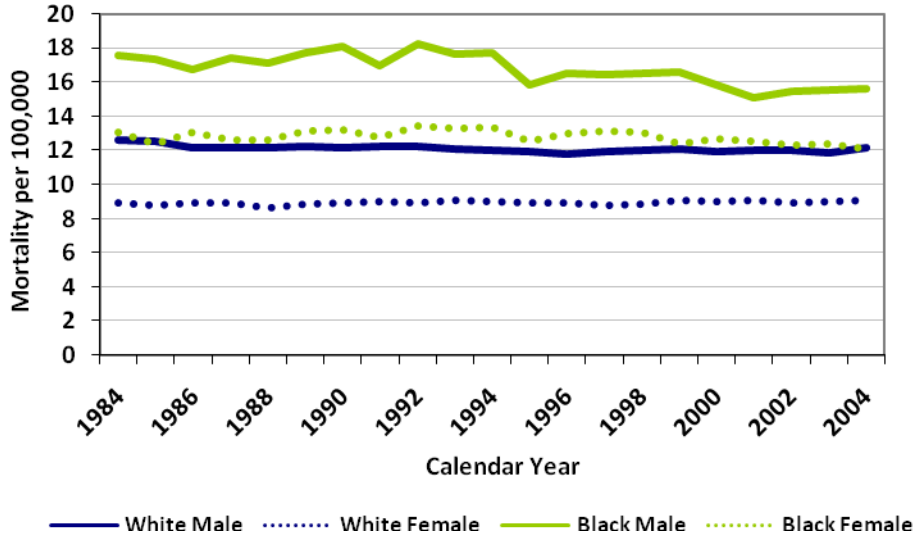


Figure 5. Male–Female Mortality Rate Trends for Pancreatic Cancer, 1984–2004
Source: NCI's SEER Program

NCI PLANNING FOR PANCREATIC CANCER RESEARCH

In 2000, the National Cancer Institute (NCI) convened the Pancreatic Cancer Progress Review Group (PRG), a multidisciplinary committee of scientists, clinicians, and advocates to review the field of pancreatic cancer research and make prioritized recommendations concerning the most urgent needs and promising directions for future NCI investment. The expertise of the PRG members was complemented by that of approximately 120 additional scientists, clinicians, and advocates who participated in a roundtable meeting on September 15–17, 2000. In February 2001, the Pancreatic Cancer PRG issued its report, *Pancreatic Cancer: An Agenda for Action.*[2] In this report, the PRG provided priority recommendations for improving the state of pancreatic cancer research in six major areas. These priority recommendations are listed in **Table 1**.

Table 1. Recommendations of the Pancreatic Cancer PRG

Priority Area	Recommendations
Health of the Field and Overarching Issues	• Develop expanded training and career development efforts • Create interdisciplinary coordinating mechanism • Establish centers of excellence
Tumor Biology	• Understand the normal biology of the pancreas • Elucidate the development of pancreatic adenocarcinoma • Study the natural history of stroma and desmoplasia • Study host-tumor interactions and develop related therapeutic strategies • Resources: Specimen banks and experimental model systems
Risk, Prevention, Screening, and Diagnosis	• Identify genetic and environmental factors that contribute to disease development • Develop approaches for prevention in high-risk cohorts • Develop early detection methods • Resources: New and expanded registries, specimen banks, large cohort consortia, education for providers and investigators about risk assessment, web-based imaging library, technology centers for assessing gene and protein expression, and animal models
Therapy	• Facilitate discovery and development of targeted therapeutics • Discover techniques to assess targeted therapeutics • Conduct research on the supportive care of patients • Resources: Investigator access to targeted therapeutic agents for research, molecular target assessment infrastructure, and multidisciplinary clinical trial infrastructure
Health Services Research	• Identify effective forms of provider/patient communication • Study message effectiveness in patient decision making • Study requirements and costs of multidisciplinary clinical trials • Evaluate current practices in diagnosis and care • Resources: Survivorship registry, web-based repository, models, education & communication tools
Scientific Toolkit	• Establish a specimen resource (normal and cancerous samples) • Develop a database of biological profiles of normal and neoplastic cells • Develop new biological sampling techniques • Capture knowledge of relevant molecular pathways • Develop gene-based model systems • Improve imaging systems

[2] Available at http://planning.cancer.gov/pdfprgreports/2001pancreatic.pdf.

NCI'S INVESTMENT IN PANCREATIC CANCER RESEARCH

This section describes NCI's progress in addressing recommendations in each of the six priority areas identified in the Pancreatic Cancer PRG report.

Health of the Field and Overarching Issues

NCI Funding for Pancreatic Cancer Research

NCI's commitment to improve the health of the pancreatic cancer research field is demonstrated by the increases in the Institute's funding for relevant research since the PRG's recommendations were made. Between FY2001 and FY2006, NCI's investment in pancreatic cancer increased by 240%, from $21.8 million to $74.2 million. The largest increase (51%) occurred in 2002, the year after the PRG report was published.

NCI's investment in pancreatic cancer-relevant research between FY2001 and FY2006 is shown in **Figure 6**. These values reflect NCI's total intramural and extramural support for pancreatic cancer research.[3] A comparison between NCI's pancreatic cancer investment and its total budget for these years is provided in **Table 2**. Since 2001 (the year the PRG report was published), the cumulative percentage increase in funding has grown at a much faster rate for pancreatic cancer than for the overall NCI budget.

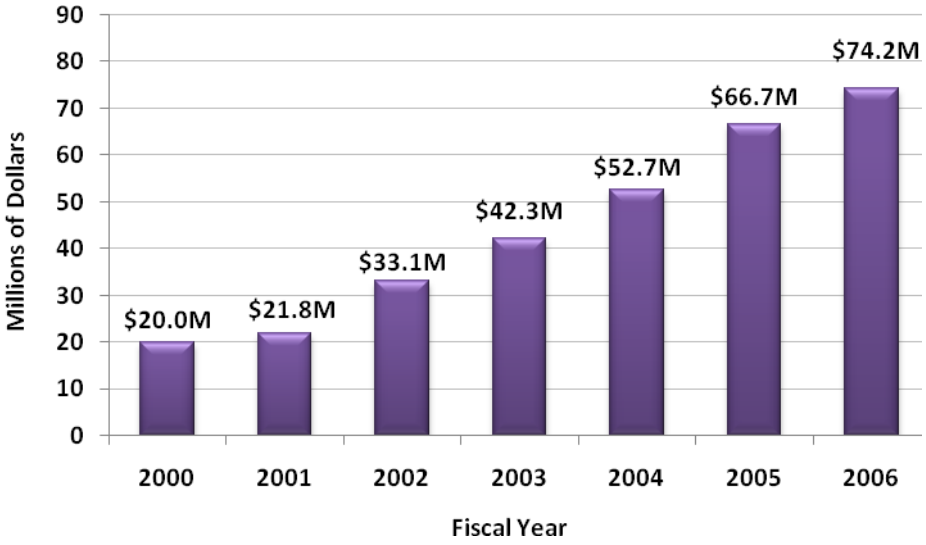


Figure 6. Trends in NCI Funding for Pancreatic Cancer Research, FY2000–FY2006

[3] As reported by the Financial Management Branch of the NCI Office of Budget and Financial Management (NCI Factbook).

Table 2. NCI's Pancreatic Cancer Research Budget, FY2000–FY2006

Fiscal Year	NCI Investment for Pancreatic Cancer ($M)	% Increase from Previous Year (cumulative % increase since 2001 PRG report)	Total NCI Budget ($M)	% Increase from Previous Year (cumulative % increase since 2001 PRG report)
2000	20.0	16% (N/A)	3,311	15% (N/A)
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2006	74.2	11% (240%)	4,747	-1% (26%)

[a] The PRG report was published in February 2001.

The majority of the NCI funds designated for pancreatic cancer research support the extramural research program. The scientific content of these projects, categorized according to the Common Scientific Outline (CSO, a classification system based on seven broad areas of scientific interest), is presented in **Figure 7**.[4] The greatest increase in NCI's investment in pancreatic cancer occurred in the treatment category; treatment spending grew from $5.3M in FY2000 to $25.5M in FY2006, an increase of 380%.

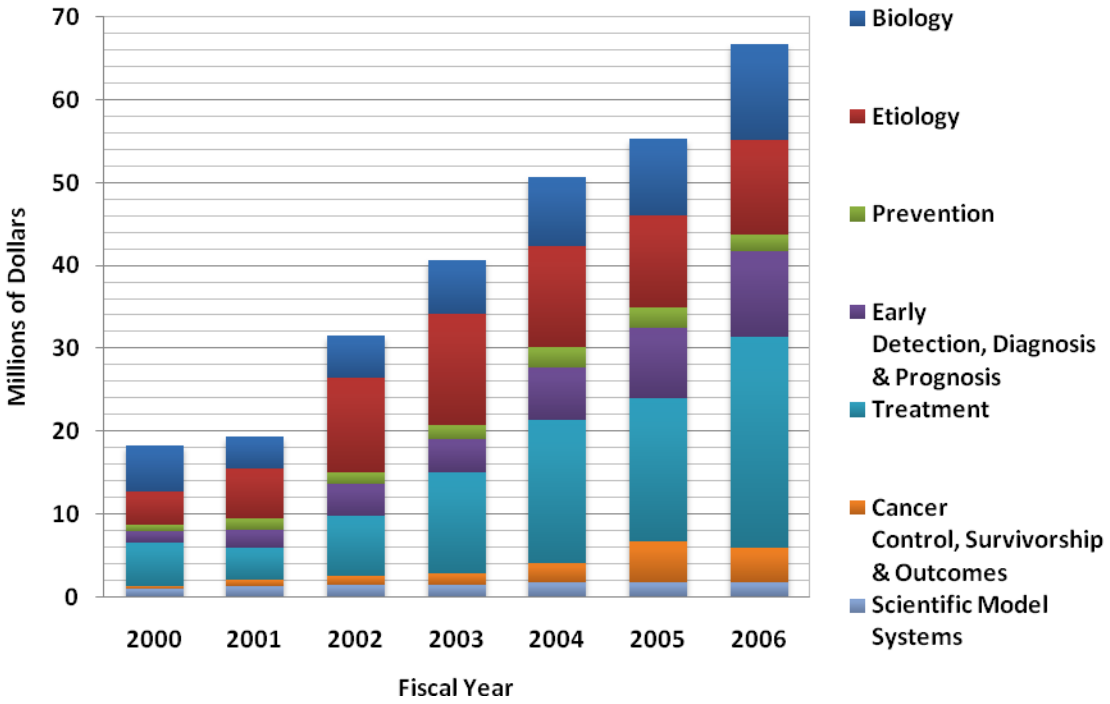

Figure 7. Dollar Estimates for Extramural Research by Scientific Area, FY2000–FY2006

[4] To derive these values, dollars associated with each funded project were prorated by estimated pancreatic cancer relevance, and this amount was equally distributed into applicable CSO research categories. Pancreatic cancer research projects were included regardless of percent relevance to pancreatic cancer, except for training grants, which are not included because percent relevance is not assigned to training grants.

Research Projects

Between FY2000 and FY2006, the number of NCI-sponsored research projects relevant to pancreatic cancer[5] has steadily increased, from 85 projects in FY2000 to 245 projects in FY2006 **(Figure 8)**. This represents an increase of 188% over the past 6 years.

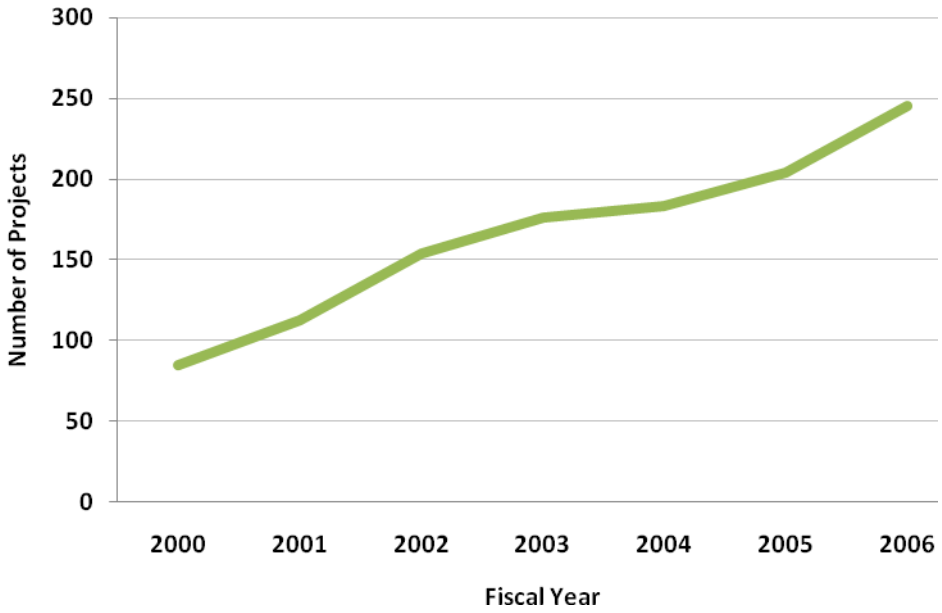

Figure 8. Total Number of NCI-Sponsored Research Projects Relevant to Pancreatic Cancer, FY2000–FY2006

The funded portfolio of pancreatic research projects was classified according to the six main PRG priority areas (**Figure 9**) and the specific recommendations in each priority area to which they are relevant (**Figures 15**, **16**, **17**, **19**, and **20**). Many projects addressed more than one PRG priority area or specific recommendation. The majority of projects funded in FY2006 were coded as being relevant to either tumor biology; risk, prevention, screening, and diagnosis; or therapy. The category with the smallest number of projects in FY2006 was health services research.

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

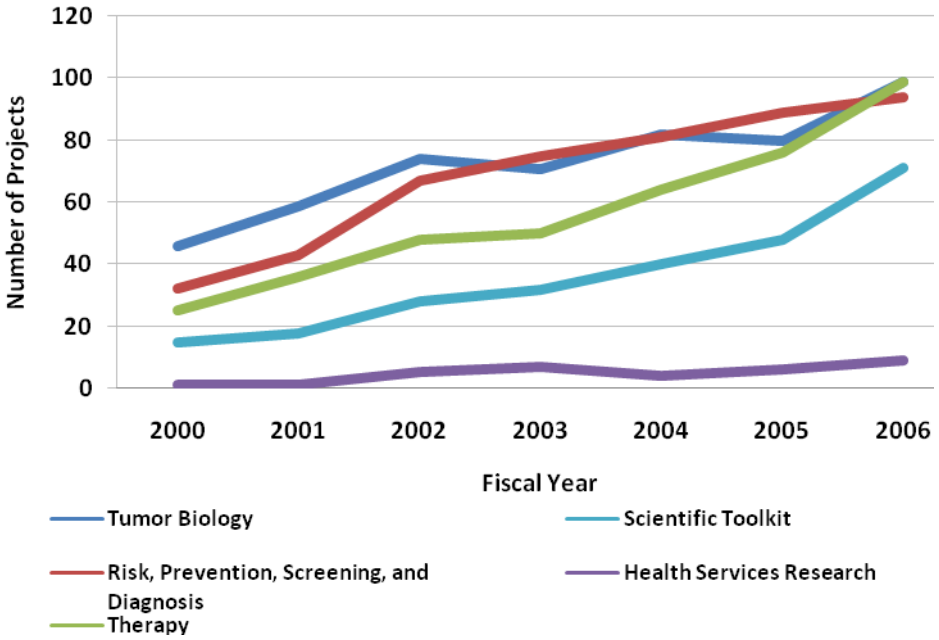

Figure 9. Pancreatic Cancer Research by PRG Category, FY2000–FY2006

Exception Funding

To address the PRG's call for increased funding for pancreatic cancer research, NCI implemented a new policy in FY2002 of increasing its payline (percentage of applications that are funded) for research that is related to pancreatic cancer. Initially, NCI's policy called for a 50% higher payline for investigator-initiated R01 grant applications with 100% relevance to pancreatic cancer. Starting in FY2004, grant applications with 50% or greater pancreatic cancer relevance were given special consideration for exception funding.

Table 3 indicates the number of projects funded under the exception funding policy in FY2002–FY2006. These projects address three of the PRG priority areas: tumor biology; risk, prevention, screening, and diagnosis; and therapy. Because of the time required to generate publishable findings and complete all of the steps in the journal peer review process, the earlier projects have produced more publications at this time than the more recently funded projects. However, over time, it is expected that most or all of these projects will generate peer-reviewed publications.

Table 3. Pancreatic Cancer Research Projects Funded under NCI's Exception Funding Policy and Resulting Publications, FY2002–FY2006

Fiscal Year	Number of Projects Funded under NCI's Exception Funding Policy	Number of Eligible Applications with Relevance to Pancreatic Cancer	Number of Resulting Publications to Date
2006	5	6	2
2005	4	8	4
2004	3	3	6
2003	4	4	43
2002	3	3	23

Source: NCI's Extramural Financial Data Branch

Clinical Trials

Between FY2000 and FY2006, NCI sponsored[6] 160 clinical trials relevant to pancreatic cancer. **Figure 10** shows the number of clinical trials that were active for each of these years according to the phase/type of trial.[7] The majority of clinical trials relevant to pancreatic cancer focus on treatment, and most of the pancreatic cancer trials during this period were either Phase I or Phase II trials. During the past 3 years, there has been a decline in the number of Phase I trials and a corresponding increase in the number of Phase II trials. There has also been an increase in diagnostic studies and clinical studies addressing end-of-life issues in this time period (represented in the "Other" category in Figure 10).

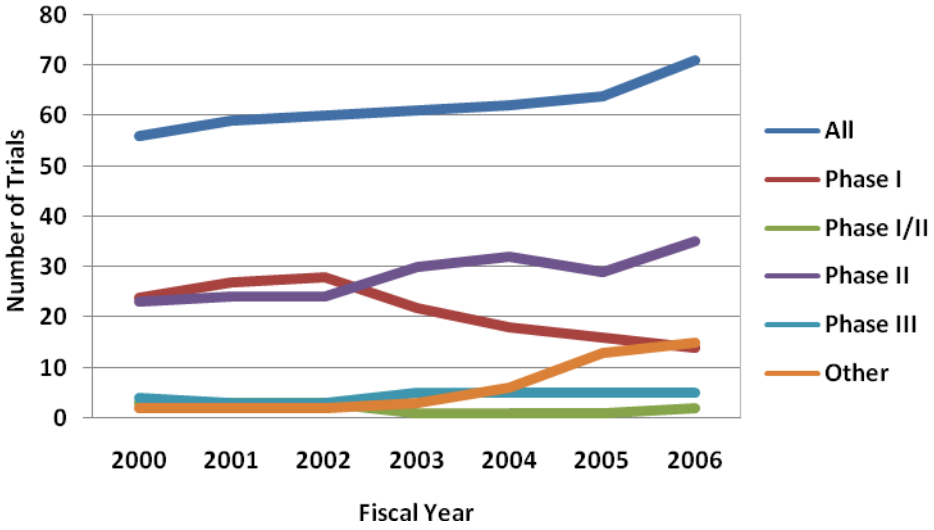

Figure 10. NCI-Sponsored Pancreatic Cancer Clinical Trials Active during FY2000–FY2006

Specialized Programs of Research Excellence (SPOREs)

SPORE grants support specialized centers that promote a bi-directional 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 share the common goal of reducing cancer incidence and mortality or improving quality of life and often involve cancer patients or populations at risk of cancer. NCI currently supports one P50 Specialized Center SPORE grant and two P20 Planning grants as well as two gastrointestinal (GI) cancer SPOREs (P50 Specialized Center grants) that have pancreatic cancer components. These SPORE programs, including the titles of their pancreatic cancer-relevant subprojects, are detailed in **Table 4**.

[6] 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 10 were active at some point during the fiscal year indicated.

[7] 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.

Table 4. SPORE Projects Related to Pancreatic Cancer

Pancreatic Cancer SPOREs			
Institution	Principal Investigator	Grant Number	Subprojects
Mayo Clinic	Gloria Petersen	P50 CA102701	• Molecular Epidemiology of Pancreatic Cancer • Characterization of the Role of BRCA2 in Pancreatic Cancer • SDF1a/CXCR4-EGFR Interactions in Pancreatic Cancer • Mechanism of VAV1-Mediated Pancreatic Cancer Cell Growth
University of Alabama at Birmingham	Donald Buchsbaum	P20 CA101955	• Mechanisms of Tumor Suppressor DPC4/Smad4 for Protein Instability in Pancreatic Cancer • Multi-modality Targeted Therapy of Pancreatic Cancer with Death Receptor Monoclonal Antibodies and Chemotherapy: Radiation Interaction
University of Texas M.D. Anderson Cancer Center	James Abbruzzese	P20 CA101936	• Role of COX-2 in Pancreatic Cancer Progression and Therapy • Development of a Novel Gene Therapy for Pancreatic Cancer • NFkB Signaling Pathways in Pancreatic Cancer Biology and Therapy • Regulation of Pancreatic Cancer Angiogenesis and Metastasis by Transcriptional Factor SP1 • DNA Repair as a Risk Factor for Pancreatic Cancer
Gastrointestinal Cancer SPORES with Pancreatic Cancer-relevant Projects			
Institution	Principal Investigator	Grant Number	Subprojects
Johns Hopkins University School of Medicine	Scott Kern	P50 CA062924	• New Genetic Clues in Pancreatic Cancer • Components of Early and Late Pancreatic Neoplasia • Screening Markers for High Pancreatic Cancer Susceptibility • Markers for the Risk in Familial Pancreatic Cancer • Integration of Chemotherapy with Vaccination in Metastatic Pancreatic Cancer
Arizona Cancer Center	Eugene Gerner	P50 CA095060	• New Molecular Targets in Colorectal and Pancreatic Cancers

Pancreatic Cancer Research Map

The Pancreatic Cancer Research Map (http://www.cancermap.org/pancreatic/index.jsp) is a new web-based tool for tracking pancreatic cancer research, clinical trials, and investigators. The map is a collaborative project between NCI, the Pancreatic Cancer Action Network (PanCAN), and the Lustgarten Foundation for Pancreatic Cancer Research.

The map is designed to meet the following goals:

- Facilitate and expedite collaborations among researchers in the pancreatic cancer research community by helping them identify developments in pancreatic cancer research and network with other researchers
- Provide a unified portfolio of cancer research, funding opportunities, and investigators, allowing interested parties to find, compare, and analyze information in ways never before possible
- Identify funding opportunities specific to pancreatic cancer research, research resources, information about investigators in the field, and reports on recent progress

Currently, the portfolio includes more than 300 research projects funded by NCI, PanCAN, and Lustgarten, as well as the American Cancer Society and the National Cancer Research Institute (United Kingdom). Analyses of research projects according to both NCI's CSO categories and the PRG's six major priority areas are available on the website. In addition, the map's investigator database contains information on more than 600 pancreatic cancer researchers.

This mapping project is led by a Steering Committee composed of members of the partner organizations and scientific experts interested in facilitating pancreatic cancer research. Members of the Pancreatic Cancer Research Map Steering Committee are:

- Dr. Tony Hollingsworth, Co-Chair, University of Nebraska
- Ms. Elizabeth Thompson, Co-Chair, PanCAN
- Dr. James Abbruzzese, M.D. Anderson Cancer Center
- Dr. Ivan Ding, NCI
- Ms. Julie Fleshman, PanCAN
- Ms. Kerri Kaplan, Lustgarten Foundation for Pancreatic Cancer Research
- Ms. Cherie Nichols, NCI
- Dr. Gloria Petersen, Mayo Clinic
- Dr. Gary Renshaw, Johnson & Johnson

The Steering Committee currently is conducting a detailed evaluation of the Research Map portfolio to assess the following:

- Completeness of the research portfolio
- Research gaps
- Progress in meeting the Pancreatic Cancer PRG recommendations
- Usefulness of the map website
- Potential improvements to the map

Growth in Numbers of Investigators

Between FY2000 and FY2006, the number of unique investigators with at least one NCI-funded R01 grant in pancreatic cancer[8,9] increased from 34 to 92, which represents a 171% increase (**Figure 11**).

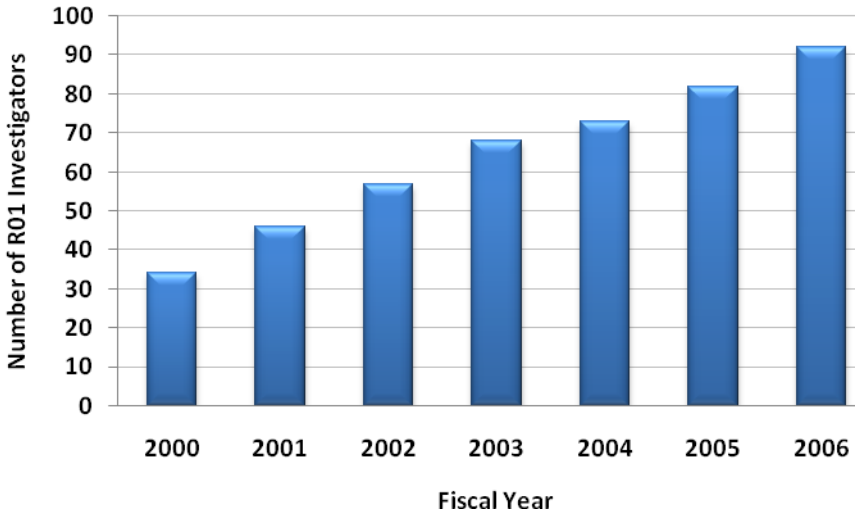

Figure 11. Number of Investigators with at Least One Pancreatic Cancer R01 Grant, FY2000–FY2006

[8] Limited to R01 grants that were at least 25% relevant to pancreatic cancer.
[9] Grants with less than 25% relevance were not included in this analysis.

Training

Grant mechanisms used by NCI for pancreatic cancer research training include F31, F32, K01, K05, K07, K08, K22, K24, K99, and T32. In FY2005, an estimated 23 distinct training projects were relevant to pancreatic cancer research and approximately $2.2 million was spent on these projects (**Figure 12**). In FY2006, an estimated 31 distinct training projects were relevant to pancreatic cancer research and approximately $2.7 million was spent on these projects. In FY2007, an estimated 36 distinct training projects were relevant to pancreatic cancer research and approximately $2.8 million was spent on these projects.[10]

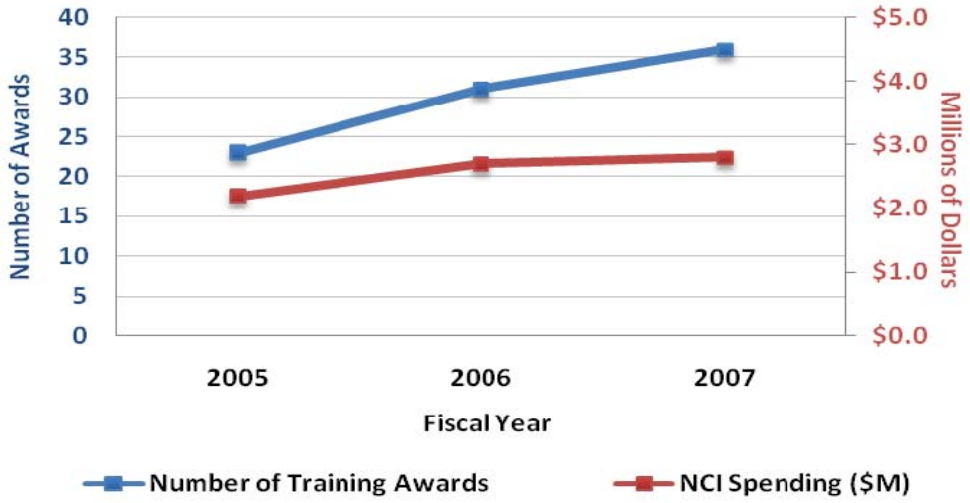

Figure 12. Training Awards for Pancreatic Cancer Research, FY2005–FY2007

[10] Limited to projects reported by NCI's Cancer Training Program and Comprehensive Minority Biomedical Branch. Does not include training supported through the SPORE program.

Research Institutions

Currently, 84 research institutions across the United States and 5 overseas institutions receive NCI funding for pancreatic cancer research.[11] The geographic breakdown of U.S. institutions that received NCI funds for pancreatic cancer research in FY2006 (25% or greater relevance to pancreatic cancer) is shown in **Figure 13**. California and Massachusetts have the highest numbers of institutions with NCI-funded pancreatic cancer research grants.

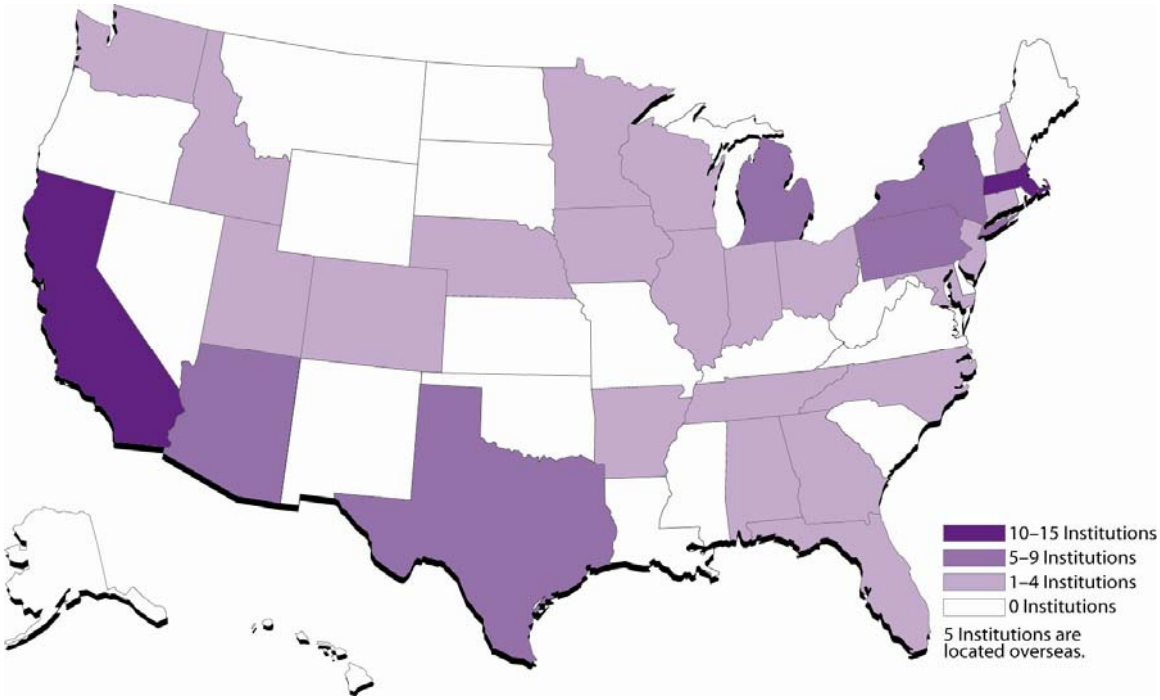

Figure 13. Distribution of NCI-Funded Institutions Conducting Pancreatic Cancer Research in FY2006

[11] Includes research funded in FY2006 that was at least 25% relevant to pancreatic cancer, as well as training and intramural projects.

Growth in Numbers of Publications

One indicator of research progress is growth in the number of peer-reviewed publications on a specific topic. The number of pancreatic cancer-relevant scientific articles acknowledging NCI support increased from 137 to 283 between calendar years 2000 and 2006 (**Figure 14**), which represents a 107% increase. These values derive from a search of the MEDLINE database[12] for abstracts that included terms related to "pancreas" and whose authors cited an NCI grant number or author address. 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.

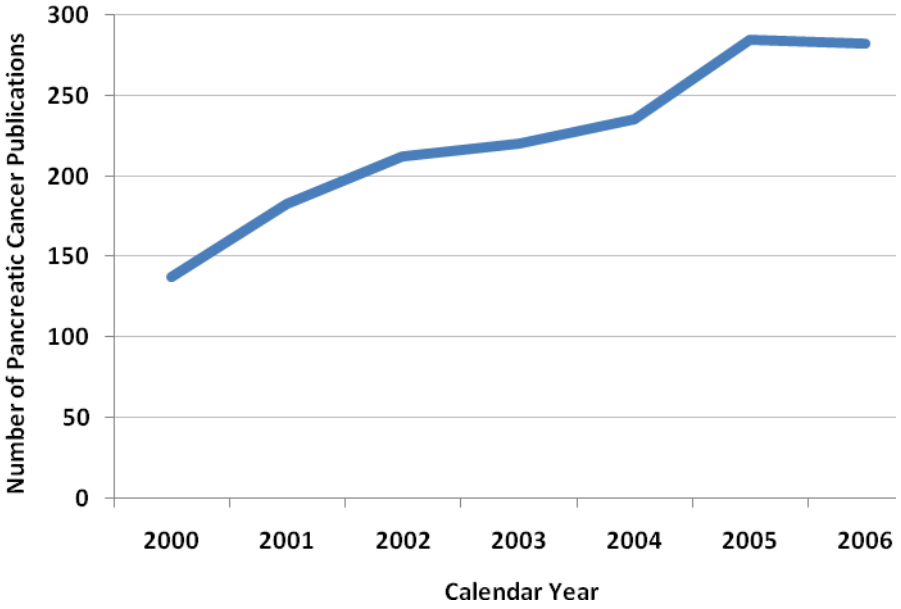

Figure 14. Estimated Number of Scientific Articles on Pancreatic Cancer Research Acknowledging NCI Support, 2000–2006

[12] Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi.

Tumor Biology

Research Projects

Between FY2000 and FY2006, there was an increase in the number of projects relevant to each of the PRG recommendations in the area of tumor biology. The majority of pancreatic cancer projects relevant to this PRG priority area addressed the development of pancreatic adenocarcinoma (**Figure 15**). The number of projects in this area increased from 34 in FY2000 to 81 in FY2006, which represents a 138% increase.

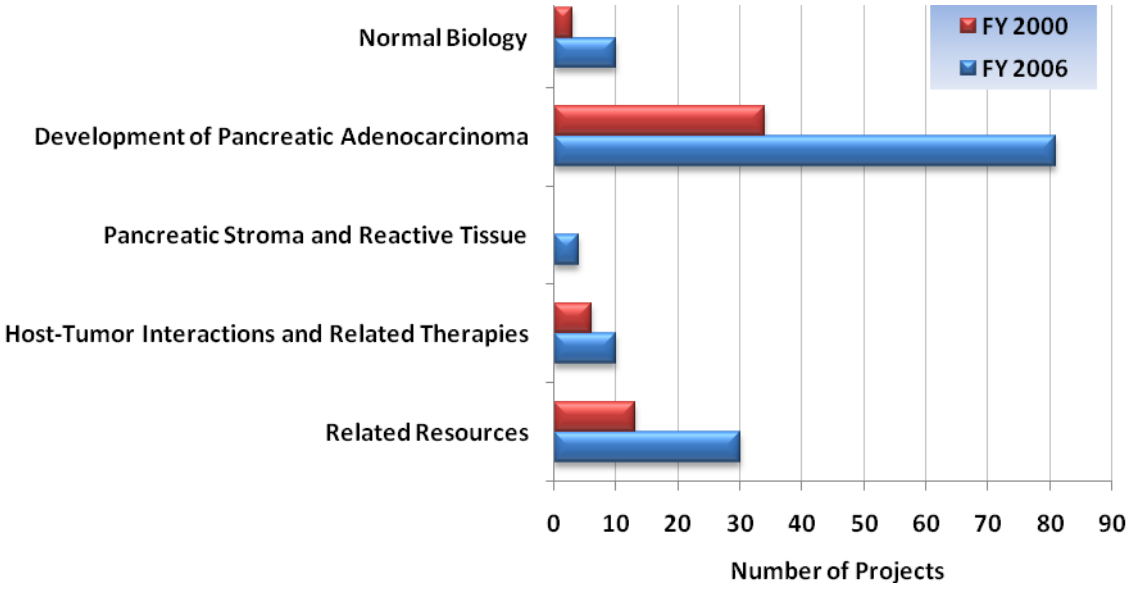

Figure 15. Pancreatic Cancer Projects Related to Tumor Biology, FY2000 and FY2006

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 addressed adequately.

NCI has established the following initiatives related to tumor biology that have funded at least one pancreatic cancer study:

- The **Howard Temin Award** bridges the transition from a mentored research environment to an independent basic cancer research career for scientists who have shown high potential during their initial training and development.
  - *This PAR (program announcement reviewed in an institute) was issued in 2003 and has funded one pancreatic cancer project to develop a new mouse model of pancreatic cancer that can be used to study the genes and processes that drive pancreatic cancer genesis and progression.*

- **Molecular and Cellular Biology of Metastatic Tumor Cells**—Fosters collaborations between investigators experienced in metastasis research and those experienced in molecular and cellular biology.
  - *This program announcement (PA) was issued in 2001 and has funded three pancreatic cancer studies on molecular determinants of pancreatic cancer cell migration and invasion.*
- **Proteomics in Diabetes and Other Endocrine and Metabolic Diseases**—Promotes the use of proteomic technologies for studying diabetes and its complications, as well as other endocrine and metabolic diseases.
  - *This PA was issued in 2003 and has funded a study focused on protein prenylation as a prognostic biomarker for pancreatic cancer patients.*
- **Ubiquitin and Ubiquitin-Like Modifications Regulating Disease Processes**—Supports studies of the roles of post-translational modifications in development, normal physiology, and/or disease progression. This initiative is jointly sponsored by NCI, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute on Aging.
  - *This PA was issued in 2006, and its predecessor has funded one study on the mechanisms of pancreatic cancer development.*
- **Pilot Studies in Pancreatic Cancer**—Promotes innovative multidisciplinary research to increase our understanding of pancreatic cancer biology, etiology, detection, prevention, and treatment.
  - *This PA was issued in 2006 and has funded 23 pancreatic cancer projects that are identifying novel pancreatic cancer therapeutic targets, predicting pancreatic tumor response to therapy, and developing new treatment strategies.*

Research Highlights

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

- **Pancreatic Cancer Stem Cells.** Experiments in mice have identified putative human pancreatic cancer stem cells that might be responsible for the development and aggressive spread of pancreatic tumors.[13]
- **Cyclin D2 Protein in Pancreatic Cancer Drug Resistance.** Pancreatic cancer is often resistant to chemotherapy, but researchers have found that overexpression of the cyclin D1 protein can contribute to drug resistance of pancreatic cancer cells. This is due to cyclin D1's dual functions—it promotes cell growth while inhibiting drug-induced cell death.[14]
- **Mn-SOD Silencing Activates Pancreatic Cancer Growth.** Researchers have discovered that silencing of the Mn-Superoxide Dismutase gene, which frequently occurs via epigenetic mechanisms in pancreatic carcinoma, renders these cells vulnerable to drugs that stimulate reactive oxygen, suggesting a potential treatment approach.

[13] Li C, Heidt DG, Dalerba P, Burant CF, Zhang L, Adsay V, Wicha M, Clarke MF, Simeone DM. Identification of pancreatic cancer stem cells. *Cancer Res.* 2007 Feb 1;67(3):1030-7.

[14] Published in Biliran H Jr, Wang Y, Banerjee S, Xu H, Heng H, Thakur A, Bollig A, Sarkar FH, Liao JD. Overexpression of cyclin D1 promotes tumor cell growth and confers resistance to cisplatin-mediated apoptosis in an elastase-myc transgene-expressing pancreatic tumor cell line. *Clin Cancer Res.* 2005 Aug 15;11(16):6075–86.

Risk, Prevention, Screening, and Diagnosis

Research Projects

A majority of projects in this priority area were related to the identification of genetic factors, environmental factors, and gene–environment interactions that contribute to pancreatic cancer development (**Figure 16**). The number of projects related to each PRG recommendation in this area increased between FY2000 and FY2006; however, the largest increase (262%) occurred in the category addressing methods for early detection of pancreatic cancer.

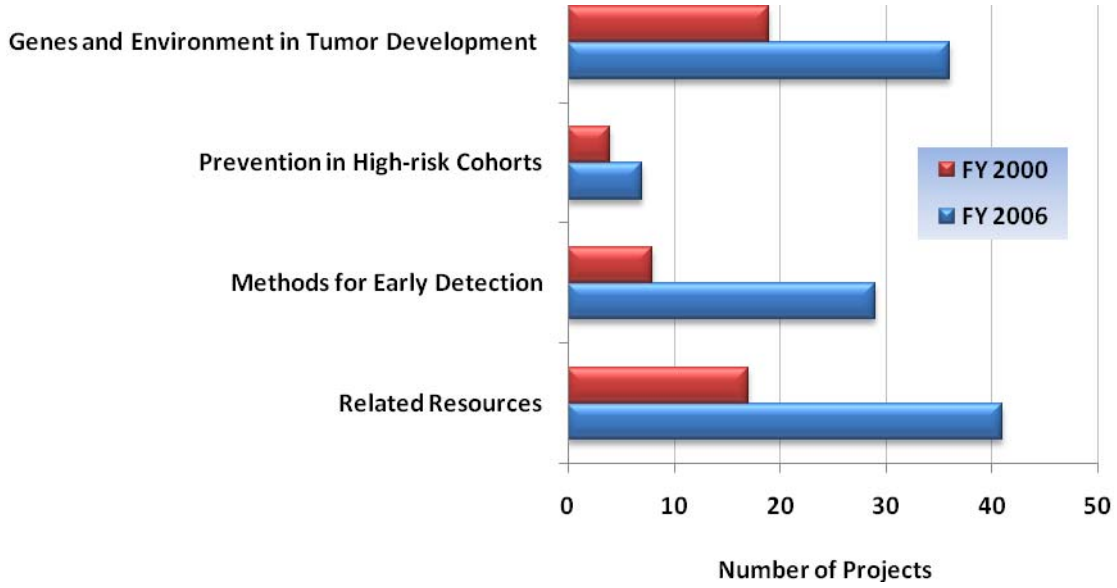

Figure 16. Pancreatic Cancer Projects Related to Risk, Prevention, Screening, and Diagnosis, FY2000 and FY2006

Clinical Trials

The number of NCI-sponsored clinical trials related to pancreatic cancer risk, prevention, screening, and diagnosis is relatively small. These studies include efforts to identify pancreatic lesions in patients with Von Hippel Lindau syndrome, Peutz-Jeghers syndrome, and relatives of patients with familial pancreatic cancer. Another study is examining whether comprehensive laparoscopic examination of the abdomen with laparoscopic ultrasonography improves staging of pancreatic cancer and predicts vascular invasion in pancreatic cancer.

Initiatives

The following initiatives related to risk, prevention, screening, and diagnosis have funded at least one pancreatic cancer study:

- The **Cancer Prevention Research Small Grant Program** supports developmental research in chemoprevention agent development, biomarkers, early detection, and nutrition science.
  - *This PAR was issued in 2006, and its predecessors have funded four pancreatic cancer studies focused on pancreatic cancer biomarkers and pathways involved in pancreatic cancer development.*
- The **Pancreatic Cancer Cohort Consortium** is conducting whole genome scans of common genetic variants to identify susceptibility markers for pancreatic cancer.
  - *This study, called PanScan, is using data from 12 prospective epidemiologic cohort studies and 1 case-control study to analyze a dense set of the most common genetic variants in the human genome.*
- **The Early Detection Research Network: Biomarker Developmental Laboratories**—Develops, evaluates, and validates biomarkers for earlier cancer detection and risk assessment.
  - *This request for applications (RFA) was issued in 2003 and has funded four pancreatic cancer studies to develop diagnostic tests and detection biomarkers for pancreatic cancer.*
- **Small Grants Program for Cancer Epidemiology**—Provides support for small projects focused on cancer etiology that may lead to cancer control/prevention.
  - *This PAR was issued in 2006, and its predecessor has funded two studies on pancreatic cancer survival and on biomarkers of pancreatic cancer risk.*
- **Molecular Approaches to Diet and Pancreatic Cancer Prevention**—Supports research on how food intake and food components influence pancreatic cancer development and prevention.
  - *This PA was issued in 2006, and its predecessors have funded three studies on the importance of energy intake and/or bioactive food constituents as site-specific modifiers of pancreatic cancer development.*

Research Highlights

Recent results of NCI-sponsored research in the risk, prevention, screening, and diagnosis of pancreatic cancer include the following:

- **Development of Nanoparticle Imaging Agent.** Researchers used a novel technique to create a multifunctional nanoparticle-based imaging agent that can help pinpoint pancreatic ductal adenocarcinoma.[15]
- **Meat and Cancer Risk.** Red and processed meat intakes were associated with an increased risk of pancreatic cancer.[16]
- **Pancreatic Cancer Biomarkers.** Researchers have identified 10 protein biomarkers in blood samples that are highly accurate at detecting pancreatic cancer and identifying truly negative samples.[17]

[15] Montet X, Weissleder R, Josephson L. Imaging pancreatic cancer with a peptide-nanoparticle conjugate targeted to normal pancreas. *Bioconjug Chem*. 2006 Jul-Aug;17(4):905-11.
[16] Nothlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN. Meat and fat intake as risk factors for pancreatic cancer: the multiethnic cohort study. *J Natl Cancer Inst.* 2005 Oct 5;97(19):1458-65.
[17] Details available in NCI Cancer Bulletin 2006, Nov. 14 26; 3(44):1-2.

- **Pancreatic Cancer Risk Association with Non-Cigarette Tobacco Products.** Cigarettes are not the only form of tobacco that may be associated with pancreatic cancer risk. A recent study showed that heavy use of smokeless tobacco and, possibly, cigar smoking may increase the risk of pancreatic cancer among those who do not smoke cigarettes.[18]
- **Genetic Basis for Familial Pancreatic Cancer Clusters.** The Johns Hopkins University GI Cancer SPORE has demonstrated a genetic basis for the familial clustering of pancreatic cancer.[19] The SPORE's patient registry will help to characterize and elucidate the epidemiological and genetic basis for this clustering. The studies are being translated to better patient care in the forms of better genetic counseling and screening for early noninvasive precancerous tumors in the pancreas.
- **Vitamin D Protects against Pancreatic Cancer.** Daily intake of vitamin D above 600 IU has been linked to a 41% reduction in pancreatic cancer risk.[20]
- **Elucidating Pancreatic Cancer Susceptibility Genes.** PACGENE is a multidisciplinary consortium of cancer institutions working to identify susceptibility genes in high-risk familial pancreatic cancer pedigrees. Recent findings indicate that those with a family history of pancreatic cancer who develop the cancer themselves do so at a significantly younger age than pancreatic cancer patients in the general population.[21]

Other Activities

The joint NCI/U.S. Food and Drug Administration (FDA) **Clinical Proteomics Program** and NCI's **Early Detection Research Network** are funding serum proteomic profiling projects for pancreatic cancer screening and early detection. The goal of the Clinical Proteomics Program is to understand, explore, and evaluate the existence of previously unknown biomarker information within serum, plasma, and other body fluids. The pancreatic cancer study was designed to use a study set of mouse samples to explore the ability of a low-molecular-weight protein information archive to classify and discriminate premalignant pancreatic cancer compared to control animals.[22]

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[18] Published in Alguacil J, Silverman DT. Smokeless and other noncigarette tobacco use and pancreatic cancer: A case-control study based on direct interviews. *Cancer Epidemiol Biomarkers Prev.* 2004 Jan;13(1):55–8.

[19] Couch FJ, Johnson MR, Rabe KG, Brune K, de Andrade M, Goggins M, Rothenmund H, Gallinger S, Klein A, Petersen GM, Hruban RH. The prevalence of BRCA2 mutations in familial pancreatic cancer. *Cancer Epidemiol Biomarkers Prev.* 2007 Feb;16(2):342-6.

[20] Skinner et al. Vitamin D intake and the risk for pancreatic cancer in two cohort studies. *Cancer Epi Biomarkers Prev.* 2006 Sept. 15(9):1688-95

[21] Petersen GM, de Andrade M, Goggins M, Hruban RH, Bondy M, Korczak JF, Gallinger S, Lynch HT, Syngal S, Rabe KG, Seminara D, Klein AP. Pancreatic cancer genetic epidemiology consortium. *Cancer Epi Biomarkers Prev.* 2006 Apr; 15 (4):704-10.

[22] This project has resulted in one publication: Hingorani SR, Petricoin EF, Maitra A, Rajapakse V, King C, Jacobetz MA, Ross S, Conrads TP, Veenstra TD, Hitt BA, Kawaguchi Y, Johann D, Liotta LA, Crawford HC, Putt ME, Jacks T, Wright CV, Hruban RH, Lowy AM, Tuveson DA. Preinvasive and invasive ductal pancreatic cancer and its early detection in the mouse. *Cancer Cell.* 2003 Dec;4(6):437-50.

Therapy

Research Projects

The majority of projects related to pancreatic cancer therapy focus on the discovery and development of targeted therapeutics (**Figure 17**). The total number of projects in this category increased from 21 projects in FY2000 to 73 projects in FY2006. The category with the largest percent increase in research projects during this time period addressed techniques to assess the targeted therapeutics. Between FY2000 and FY2006, there was a 293% increase in projects relevant to this category.

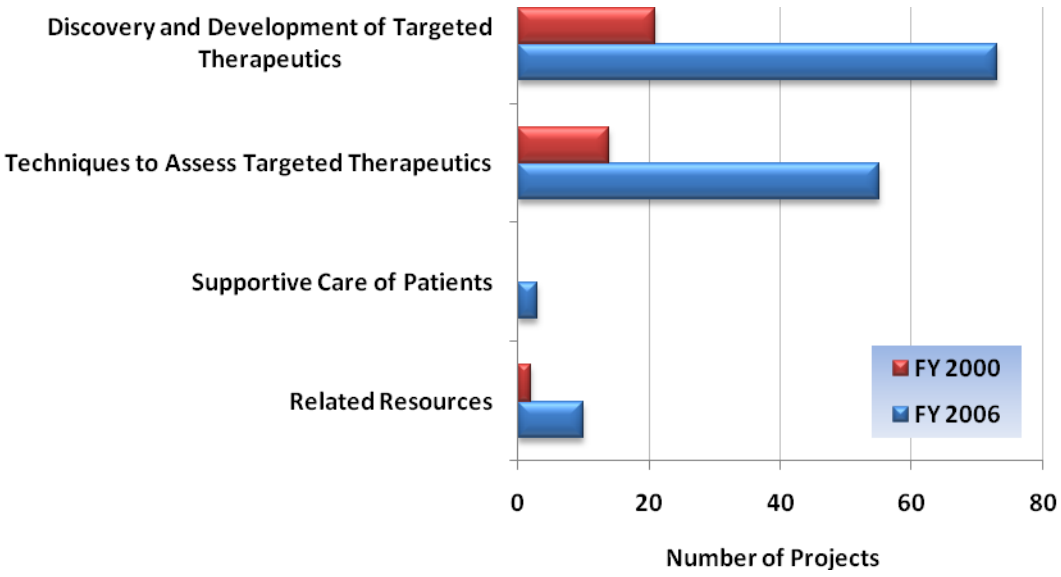

Figure 17. Pancreatic Cancer Projects Related to Therapy, FY2000 and FY2006

Clinical Trials

The number of NCI-sponsored clinical trials related to pancreatic cancer therapy increased slightly in 2003, the year that the Pancreatic Cancer PRG report was published, and has remained relatively stable since then (**Figure 18**). NCI sponsors many more trials related to pancreatic cancer treatment than supportive care.[23]

[23] Given pancreatic cancer's low survival rate, NCI sponsors a relatively larger number of treatment trials.

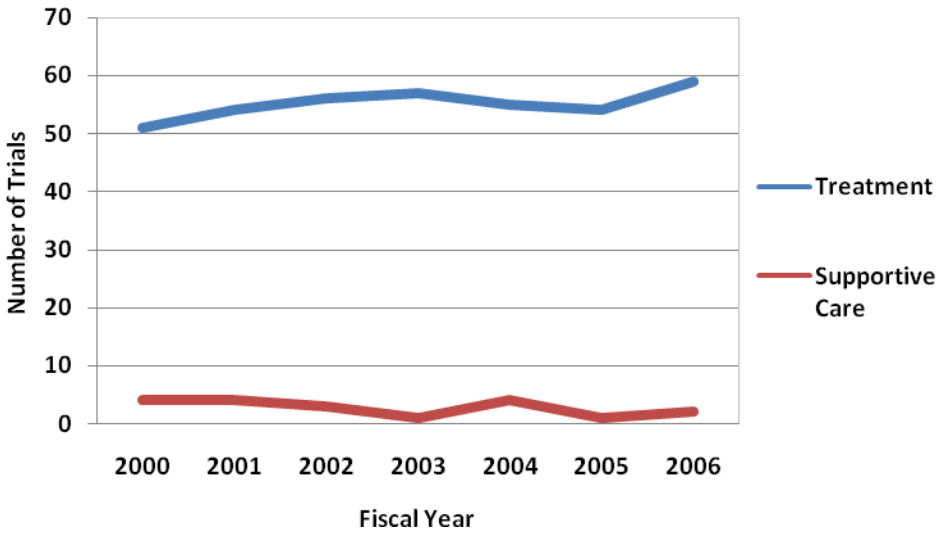

Figure 18. Pancreatic Cancer Clinical Trials Related to Therapy, FY2000–FY2006

Several ongoing NCI-sponsored clinical trials are evaluating novel agents and novel combinations of agents for treating pancreatic cancer. These trials were initiated as a result of NCI's emphasis on pancreatic cancer research. They represent a true achievement of the investigators involved because they were all large randomized trials, involved new chemotherapeutic and biologic agents, and accrued participants extremely rapidly. In particular, since the Pancreatic Cancer PRG report was issued in 2002, the NCI-sponsored Cooperative Group clinical trials program developed and implemented three large randomized Phase III trials (listed below) to evaluate new cytotoxic and biologic agents in patients with advanced and metastatic pancreatic cancer. These trials are some of the largest Phase III trials conducted in this disease site.

- ***Randomized Study of Gemcitabine [fixed-dose rate infusion] and Oxaliplatin versus Gemcitabine [fixed-dose rate infusion] versus Gemcitabine [30-minute infusion] in Pancreatic Carcinoma***—This trial is designed to evaluate the potential efficacy of fixed-dose-rate gemcitabine and fixed-dose-rate gemcitabine in combination with oxaliplatin compared to standard gemcitabine therapy alone in patients with advanced or metastatic pancreatic cancer. This trial enrolled 833 patients between 2003 and 2005.[24]
- ***Gemcitabine with or without Cetuximab as First-Line Therapy in Treating Patients with Locally Advanced Unresectable or Metastatic Adenocarcinoma of the Pancreas***—This trial is designed to evaluate the potential efficacy of the monoclonal antibody cetuximab (which targets the EGFR) in combination with gemcitabine compared to standard gemcitabine therapy alone in patients with advanced or metastatic pancreatic cancer. This trial enrolled approximately 750 patients between 2004 and 2006.[25]

[24] E. Poplin, D. E. Levy, J. Berlin, M. L. Rothenberg, P. J. O'Dwyer, D. Cella, E. Mitchell, S. Alberts and A. Benson, III. Phase III trial of gemcitabine (30-minute infusion) versus gemcitabine (fixed-dose-rate infusion [FDR]) versus gemcitabine + oxaliplatin(GEMOX) in patients with advanced pancreatic cancer (E6201). [Abstract] *J Clin Oncol* 24 (Suppl 18): LBA4004, 180s, 2006. 2007 Feb 15;109(4):796-801.

[25] Philip PA, Benedetti J, Fenoglio-Preiser C, Zalupski M, Lenz H, O'Reilly E, Wong R, Atkins J, Abruzzese J and Blanke C. Phase III study of gemcitabine [G] plus cetuximab [C] versus gemcitabine in patients [pts] with locally

- ***Gemcitabine with or without Bevacizumab in Treating Patients with Locally Advanced or Metastatic Pancreatic Cancer***—This trial is designed to evaluate the potential efficacy of the monoclonal antibody bevacizumab (which targets the vascular endothelial growth factor, a protein that plays an important role in tumor angiogenesis and maintenance of existing tumor vessels) in combination with gemcitabine compared to standard gemcitabine therapy alone in patients with advanced or metastatic pancreatic cancer. This trial enrolled approximately 602 patients between 2004 and 2006.[26]

In addition, the Cooperative Groups and the multicenter Phase II consortia sponsored by the CTEP Investigational Drug Branch have conducted several Phase II trials to evaluate new investigational agents in pancreatic cancer. Currently, 10 Phase II trials are evaluating novel agents for the treatment of patients with pancreatic cancer, including 17-AAG, Su11248, sorafenib, AZ 2171, and PS 341. These trials also are testing combinations of molecularly targeted agents with chemotherapy, such as bevacizumab plus cetuximab with gemcitabine, and bevacizumab plus erlotinib with gemcitabine. The target enrollment for these 10 trials is approximately 500 patients.

Initiatives

NCI has established the following therapy-related initiatives that have funded at least one pancreatic cancer study:

- The **Innovative and Exploratory Research in Digestive Diseases and Nutrition** initiative is sponsored by NCI and the National Institute of Diabetes and Digestive and Kidney Diseases. It stimulates the development of highly novel scientific ideas, model systems, tools, agents, targets, and technologies that have the potential to substantially advance biomedical research in digestive diseases and nutrition.
  - *This PA was issued in 2006, and its predecessor has funded two pancreatic cancer studies to develop therapeutic agents for pancreatic cancer.*
- The **Flexible System to Advance Innovative Research (FLAIR) for Cancer Drug Discovery by Small Businesses** provides flexible support that small businesses need to bring their innovative drug discovery and development efforts to clinical validation.
  - *This PA was issued in 2003 and, along with its predecessors, has funded four pancreatic cancer studies that are developing mouse models for research on pancreatic cancer therapies and evaluating novel therapeutic agents for pancreatic cancer.*
- **Rapid Access to Intervention Development (RAID)**—Efficiently moves novel treatment interventions developed in academic settings into the clinic.
  - *Seven of the projects supported by RAID focus on pancreatic cancer.*
- **Quick Trials for Novel Cancer Therapies**—Provides investigators with rapid access to support for pilot, Phase I, and Phase II cancer clinical trials and associated patient monitoring and laboratory studies to ensure the timely development of new therapeutic approaches.

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advanced or metastatic pancreatic adenocarcinoma [PC]: SWOG S0205 study. [Abstract] *J Clin Oncol* 25 (Suppl 18): LBA4509, 2007.

[26] Philip PA, Benedetti J, Fenoglio-Preiser C, Zalupski M, Lenz H, O'Reilly E, Wong R, Atkins J, Abruzzese J and Blanke C. Phase III study of gemcitabine [G] plus cetuximab [C] versus gemcitabine in patients [pts] with locally advanced or metastatic pancreatic adenocarcinoma [PC]: SWOG S0205 study. [Abstract] *J Clin Oncol* 25 (Suppl 18): LBA4509, 2007.

- *This PA was issued in 2006, and its predecessors have funded six clinical trials of pancreatic cancer therapies.*

- The **Pilot Studies in Pancreatic Cancer** initiative promotes innovative multidisciplinary research to better understand the biology, etiology, detection, prevention, and treatment of pancreatic cancer.
  - *This PA was issued in 2005 and has funded 14 studies on targets for pancreatic cancer treatment, mouse models for research on pancreatic cancer therapies, and potential new pancreatic cancer therapies.*

Research Highlights

Recent results of NCI-sponsored research in pancreatic cancer therapy include the following:

- **Addition of Gemcitabine to Standard Therapy.** When the chemotherapy drug gemcitabine was added to the standard combination of radiation therapy and the drug 5-fluorouracil, overall survival improved in patients with pancreatic tumors located in the head of the pancreas.[27]
- **Genetic Differences Can Affect Treatment Response and Survival.** Genetic variations in drug metabolism, DNA damage response, and DNA repair affect clinical response to pancreatic cancer therapy and could affect patient survival.[28]
- **Erlotinib with Gemcitabine as First-Line Pancreatic Cancer Therapy.** A recent clinical trial found that patients with advanced pancreatic cancer who were treated with the drug erlotinib in addition to gemcitabine had modest improvement in 1-year survival rates compared to patients treated with gemcitabine alone.[29] The FDA recently approved erlotinib in combination with gemcitabine as a first-line treatment for patients with advanced, inoperable, or metastatic pancreatic cancer.
- **Endoplasmic Reticulum (ER) Stress Role in Pancreatic Cancer Cell Death.** Evidence indicates that pancreatic cancer cells are uniquely sensitive to ER stress. According to a study by the M.D. Anderson Cancer Center, ER stress plays a role in cell death in human pancreatic cancer cells exposed to bortezomib.[30,31]
- **Longer Disease-Free Survival after Surgery with Adjuvant Gemcitabine Therapy.** Chemotherapy with gemcitabine is standard therapy in advanced, inoperable pancreatic cancer but until recently, the value of adjuvant therapy had not been clearly defined. A recent evaluation of the efficacy and toxicity of adjuvant gemcitabine showed that patients with resected pancreatic cancer who were treated with gemcitabine 6 months after resection experienced increased disease-free survival.[32]

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[27] NCI Clinical Trials Results. June 5, 2006.
[28] Li D, Okazaki T, Suzuki H, Javle M, Jiao L, Evans D, Abbruzzese JL. Genetic variations in drug metabolism and DNA damage response and repair as predictors of outcomes of pancreatic adenocarcinoma. SPORE Investigators Workshop. July 2007.
[29] Details available in Erlotinib Plus Gemcitabine Boosts One-Year Survival in Pancreatic Cancer, Clinical Trial Results, www.cancer.gov.
[30] Nawrocki ST, Carew JS, Pino MS, Highshaw RA, Dunner K Jr, Huang P, Abbruzzese JL, McConkey DJ. Bortezomib sensitizes pancreatic cancer cells to endoplasmic reticulum stress-mediated apoptosis. *Cancer Res*. 2005 Dec 15;65(24):11658-66.
[31] Nawrocki ST, Carew JS, Dunner K Jr, Boise LH, Chiao PJ, Huang P, Abbruzzese JL, McConkey DJ. Bortezomib inhibits PKR-like endoplasmic reticulum (ER) kinase and induces apoptosis via ER stress in human pancreatic cancer cells. *Cancer Res*. 2005 Dec 15;65(24):11510-9
[32] Details available in NCI Cancer Bulletin 2005, May 17, 2(20): 5.

- **Survival Nearly Doubled with Adjuvant Gemcitabine Compared to Surgery Alone.** In a large randomized clinical trial, patients with operable pancreatic cancer who received adjuvant therapy with the drug gemcitabine lived nearly twice as long before their disease recurred as patients who were treated with surgery alone.[33]
- **Anti-Mesothelin Antibody Shows Promise for Treating Pancreatic Cancer.** A Phase I clinical study showed that treatment with antibodies against the mesothelin protein, which is upregulated in pancreatic cancer cells, was well tolerated and shows promise for treating pancreatic cancer and other mesothelin-expressing cancers.[34]

[33] Details available in Post-Surgery Gemcitabine Delays Recurrence of Pancreatic Cancer, Clinical Trial Results, cancer.gov.

[34] Hassan R, Bullock S, Premkumar A, Kreitman RJ, Kindler H, Willingham MC, Pastan. Phase I study of SS1P, a recombinant anti-mesothelin immunotoxin given as a bolus I.V. infusion to patients with mesothelin-expressing mesothelioma, ovarian, and pancreatic cancers. *Clin Cancer Res.* 2007 Sep 1;13(17):5144-9.

Health Services Research

Research Projects

Although a smaller number of pancreatic cancer projects are related to health services research (**Figure 19**) than any of the other PRG priority areas, the number of projects related to this group of recommendations did increase between FY2000 and FY2006.[35] In particular, the category of research with the largest increase in projects was health services research resources, which include a survivorship registry, a web-based repository, new models, and education and communication tools.

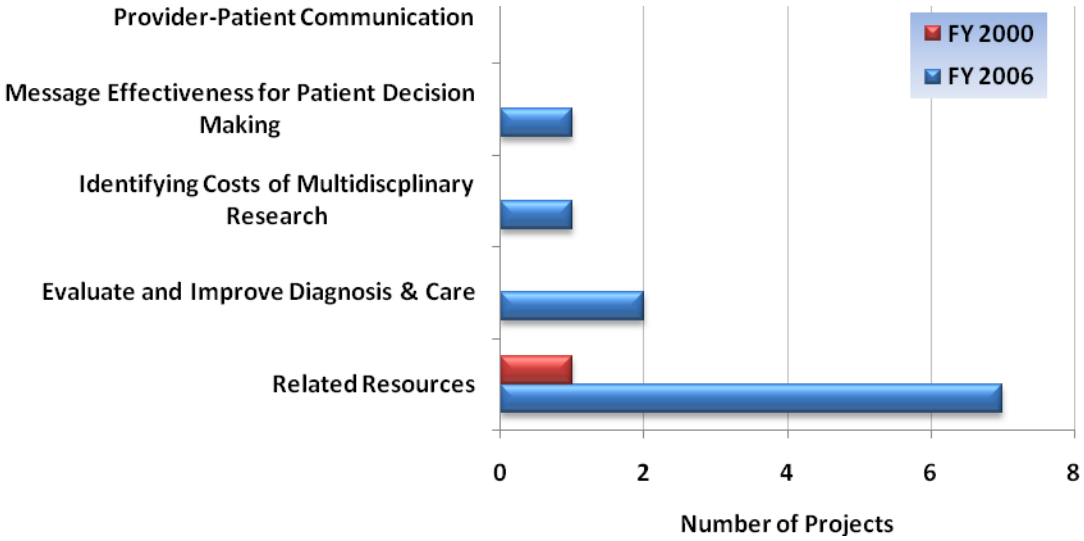

Figure 19. Pancreatic Cancer Projects Related to Health Services Research, FY2000 and FY2006

Initiatives

NCI has established the following health services research-related initiatives:

- The **Cancer Surveillance Using Health Claims-based Data System**, sponsored by NCI and the Agency for Healthcare Research and Quality, supports research using health claims data for cancer surveillance.
  - *This PA was issued in 2006, and its predecessor funded a study on variations in treatment for pancreatic cancer.*
- The **Understanding and Promoting Health Literacy** initiative encourages empirical research on health literacy concepts, theory, and interventions.
  - *This PA was issued in 2006, and its predecessor has funded one pancreatic cancer study on the impact of health literacy on pancreatic cancer outcomes.*

[35] Health services research related to pancreatic cancer is also being conducted by the American Cancer Society and Agency for Healthcare Research and Quality.

Research Highlights

Patients who had surgery for pancreatic cancer at facilities with on-site radiation services were almost twice as likely to receive adjuvant radiotherapy as those treated at a facility without such services.[36]

[36] Wong SL, Wei Y, Birkmeyer JD. Use of adjuvant radiotherapy at hospitals with and without on-site radiation services. *Cancer.* 2007 Feb 15;109(4):796-801.

Scientific Toolkit

Research Projects

The number of projects related to the pancreatic cancer scientific toolkit increased substantially between FY2000 and FY2006 (**Figure 20**), with increases for each of the PRG recommendations in this priority area except for organization of signal transduction knowledge, which has no related projects. The largest increase was seen in the number of projects addressing in vivo and ex vivo gene-based model systems that faithfully parallel the complex biology of the human pancreas. Between FY2000 and FY2006, the number of projects in this category increased by 260%, from 10 projects to 36 projects.

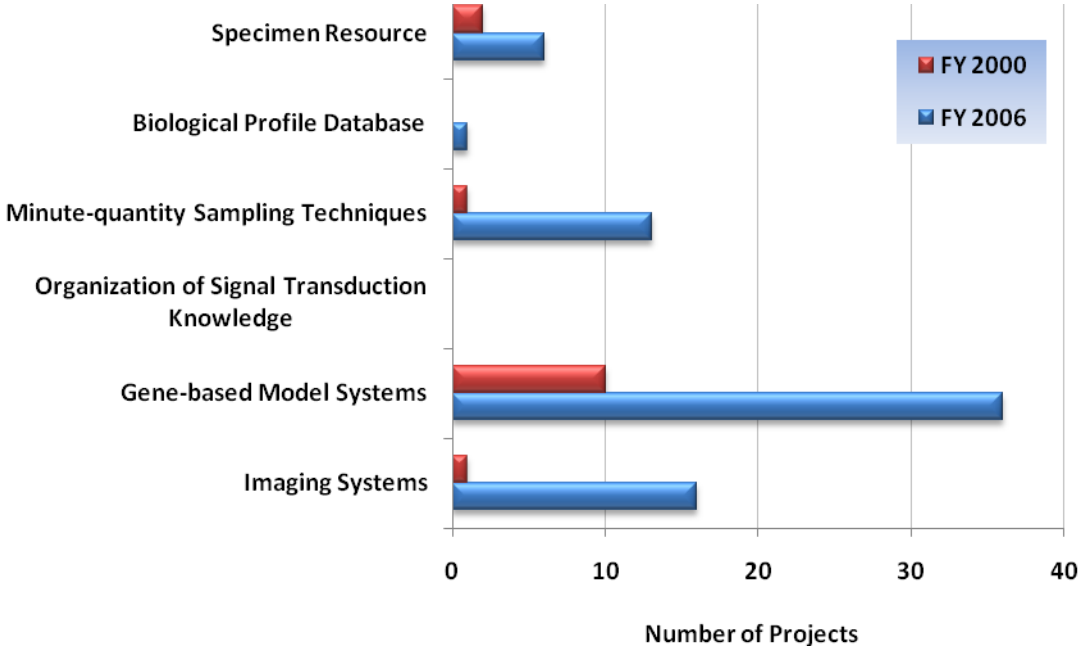

Figure 20. Pancreatic Cancer Projects Related to Scientific Toolkit, FY2000 and FY2006

Initiatives

NCI has established the following initiatives related to the scientific toolkit that have funded at least one pancreatic cancer study:

- The **Application of Emerging Technologies for Cancer Research** evaluates the usefulness of emerging technologies that can be used to answer clinical or biological questions in cancer research.
  - *This RFA was issued in 2007, and its predecessors have funded three pancreatic cancer studies that are developing new techniques to detect pancreatic cancer and new methods to study pancreatic cancer biology.*

- The **Cancer Nanotechnology Platform Partnerships** develop nanotechnology platforms for basic, applied, and translational cancer research using nanoscale devices or nanomaterials.
  - *This RFA was issued in 2004 and has funded two pancreatic cancer studies that are developing nanoparticles for use in treatment and diagnosis, and studying environmental and genetic factors that influence a person's susceptibility to DNA changes that can lead to pancreatic cancer.*
- **Mouse Models of Human Cancers Consortium** initiative has supported the development of several mouse models that may provide insight into pancreatic cancer in humans.
  - *This RFA was issued in 2003 and has funded four projects to develop mouse models to facilitate gene discovery, understand the genetic and environmental factors that influence pancreatic tumor formation, and enhance anti-tumor immunity in the mouse.*
- **Novel Technologies for In Vivo Imaging**—Supports the development and delivery of novel image acquisition or enhancement technologies and methods for biomedical imaging and image-guided interventions and therapy.
  - *This PAR was issued in 2006, and its predecessors have funded three projects that are developing new animal models and corresponding techniques for real-time imaging of pancreatic cancer growth, metastasis, tumor regression, or expression of associated biomarkers.*

Research Highlights

Recent results of NCI-sponsored research in the scientific toolkit for pancreatic cancer include:

- **Mouse Model Elucidates Joint Action of Mutated Genes That Promote Pancreatic Cancer.** Scientists have developed a bioengineered mouse model containing two "signature mutations" seen in the human form of pancreatic cancer. Just as they do in humans, the mutated genes in the mouse model work together to allow the development of premalignant lesions, which in turn lead to full-blown disease.[37]
- **Gene Mutation in Mouse Model Leads to Premalignant Pancreatic Lesions and Proteomic Marker Identification.** A second new pancreatic cancer mouse model, which contains a gene mutation similar to that seen in human pancreatic cancer, develops premalignant lesions similar to those occurring in humans. The research team also found a proteomic signature that could be used to detect the presence of the precancerous lesion in serum samples.[38]
- **Mouse Model of Pancreatic Cancer with Pancreatic Expression of Thymidylate Synthase.** Researchers have developed a mouse model of pancreatic cancer induced by high levels of thymidylate synthase, an enzyme that helps regulate DNA synthesis during cell division.

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[37] Published in Aguirre AJ, Bardeesy N, Sinha M, Lopez L, Tuveson DA, Horner J, Redston MS, DePinho RA. Activated Kras and Ink4a/Arf deficiency cooperate to produce metastatic pancreatic ductal adenocarcinoma. *Genes Dev.* 2003 Dec 15;17(24):3112–26. Epub 2003 Dec 17.

[38] Published in Hingorani SR, Petricoin EF, Maitra A, Rajapakse V, King C, Jacobetz MA, Ross S, Conrads TP, Veenstra TD, Hitt BA, Kawaguchi Y, Johann D, Liotta LA, Crawford HC, Putt ME, Jacks T, Wright CV, Hruban RH, Lowy AM, Tuveson DA. Preinvasive and invasive ductal pancreatic cancer and its early detection in the mouse. *Cancer Cell* 2003 Dec;4(6): 437–50.

CONCLUSION

NCI continues to invest in research that will help implement the recommendations of the Pancreatic Cancer Progress Review Group. For example, NCI's major new initiatives—including the NCI Alliance for Nanotechnology in Cancer and the Cancer Biomedical Informatics Grid (caBIG)—hold tremendous promise for improving and extending the lives of people with pancreatic cancer. In addition, the 71 currently active pancreas-related clinical trials sponsored by the Institute—often in partnership with other organizations—provide numerous opportunities to identify safer and more effective treatments for the disease and even prevent its occurrence. In the coming years, NCI will build on the new knowledge and new technologies these efforts will produce and maintain its commitment to ensure that the results of research are translated rapidly into practice so that they can truly make a difference in the lives of those affected by pancreatic cancer.