National Cancer Institute

Pancreatic Cancer: Five Years of Research Progress

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U.S. DEPARTMENT OF
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National Institutes of Health

Pancreatic Cancer: Five 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 5 years in each of these areas.

Approach

A retrospective analysis performed in 2006 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 5 years, NCI funding for pancreatic cancer increased by more than 200%. The number of pancreatic cancer research projects grew substantially in all of the PRG priority areas except health services research, possibly because individuals with this disease do not typically survive for long periods of time. In the coming years, NCI will continue striving 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 5-year progress in pancreatic cancer found that:

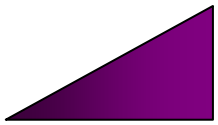
- **Since the 2001 Pancreatic Cancer PRG report was published, NCI's investment in pancreatic cancer research grew by 206%, from $21.8 million to $66.7 million**. In comparison, the total NCI budget increased by 28% during this period.
- **The number of funded investigators with NCI-funded R01 grants increased by 141% between FY2000 and FY2005**. The greatest increase occurred for researchers whose grants had the highest levels of relevance to pancreatic cancer.

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%)

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

Progress was also made in the following overarching areas:

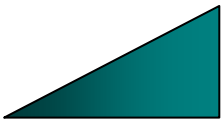
***Number of Research Projects**[a] (FY2000–FY2005)*



85 Projects — 204 Projects

↑ 140%

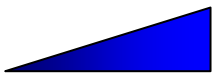
***Number of Investigators with NCI-Funded R01 Grants** (FY2000–FY2005)*



34 Investigators — 82 Investigators

↑ 141%

***Number of Scientific Articles Acknowledging NCI Support** (CY2000–CY2005)*



137 Articles — 248 Articles

↑ 81%

[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 Program of Research Excellence (SPORE) programs are not included in the project counts.

Additional NCI Activities to Advance Pancreatic Cancer Research Include:

Exception Funding

Since the 2001 PRG, NCI has funded 14 pancreatic cancer research projects (out of 18 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 FY2005, 129 NCI-sponsored clinical trials relevant to pancreatic 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 (SPOREs)

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

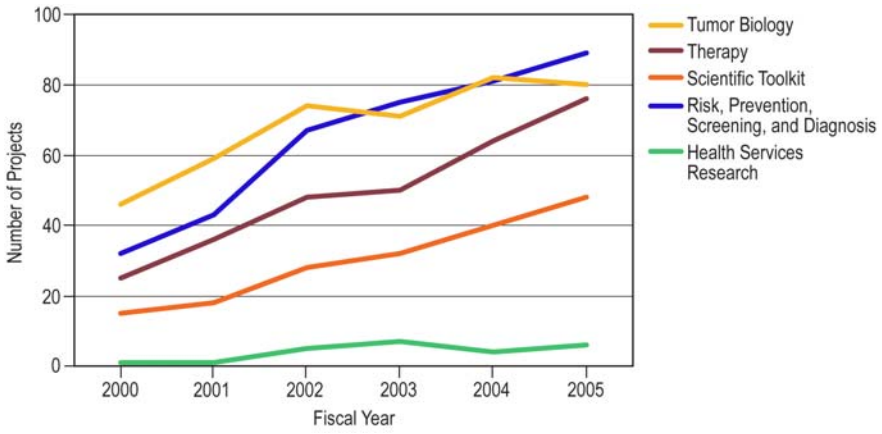
NCI-Funded Institutions

Currently, 77 U.S. research institutions and 1 overseas institution 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 FY2005:



[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:

- Men who reported using medication to treat their diabetes had more than two and a half times the risk of developing pancreatic cancer compared to men without diabetes.
- Nonsmokers who are heavy smokeless tobacco users may have an increased risk of pancreatic cancer.

Therapy:

- Patients with advanced pancreatic cancer treated with the drug erlotinib in addition to gemcitabine had modest improvement in 1-year survival rates.
- Endoplasmic reticular stress plays a role in cell death in human pancreatic cancer cells exposed to bortezomib.

Scientific Toolkit:

- A new pancreatic-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.

Pancreatic Cancer: Five Years of Research Progress

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 2006, an estimated 33,730 individuals will be diagnosed with pancreatic cancer, and an estimated 32,300 deaths will occur as a result of this disease. The total number of pancreatic cancer cases and deaths has increased since 2003 (**Figure 1**). However, in the past 20 years, the overall incidence rate has decreased very slightly (**Figure 2**).

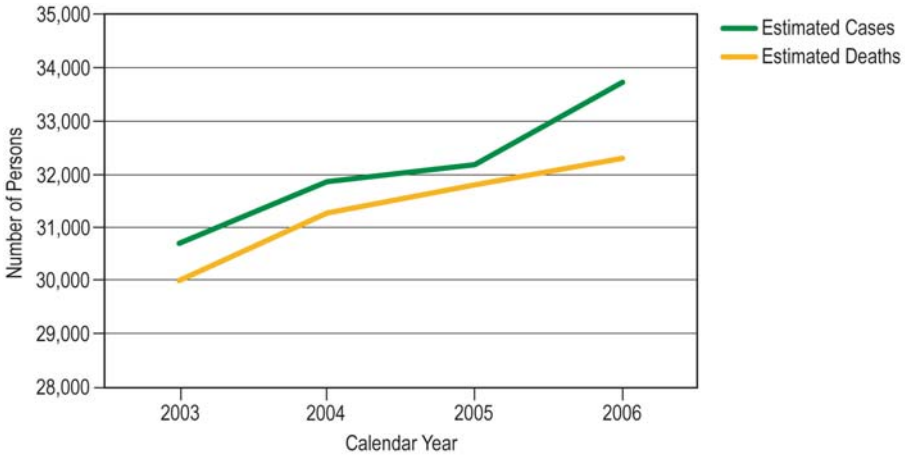


Figure 1. Pancreatic Cancer Estimated New Cases and Deaths by Year, 2003–2006
Source: American Cancer Society: Cancer Facts and Figures 2003, 2004, 2005, 2006
Available at: http://www.cancer.org/docroot/STT/STT_0.asp

Most of the observed decrease in overall pancreatic cancer incidence rates over the past 20 years reflects lower incidence among African Americans (**Figure 2**), the racial/ethnic group with the highest pancreatic cancer incidence rate. Although whites, Hispanics, Asians/Pacific Islanders, and American Indians/ Alaska Natives are less likely to develop pancreatic cancer than African Americans, overall incidence rates in these populations have not changed in recent years.

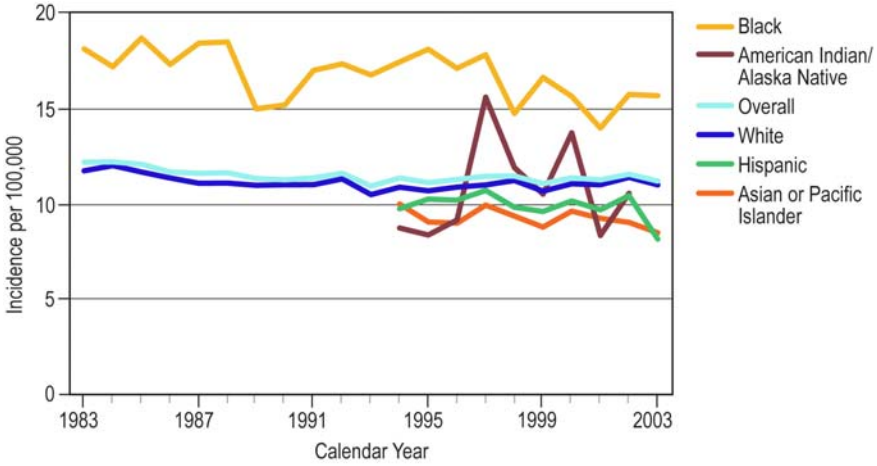


Figure 2. Pancreatic Cancer Incidence Rate Trends by Racial/Ethnic Group, 1983–2003
Source: NCI's Surveillance, Epidemiology, and End Results (SEER) Program

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

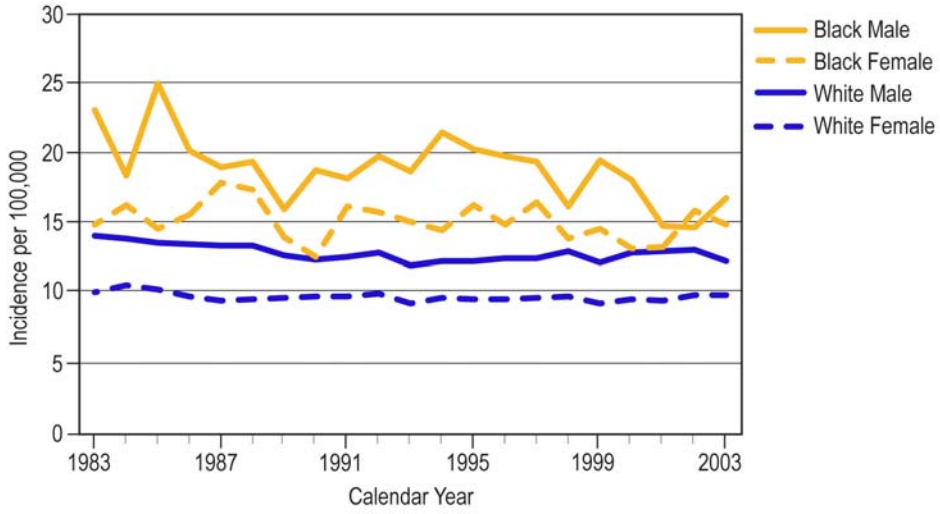


Figure 3. Pancreatic Cancer Male–Female Incidence Rate Trends, 1983–2003
Source: NCI's Surveillance, Epidemiology, and End Results (SEER) Program

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 males than 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 is seldom diagnosed before it has spread extensively.

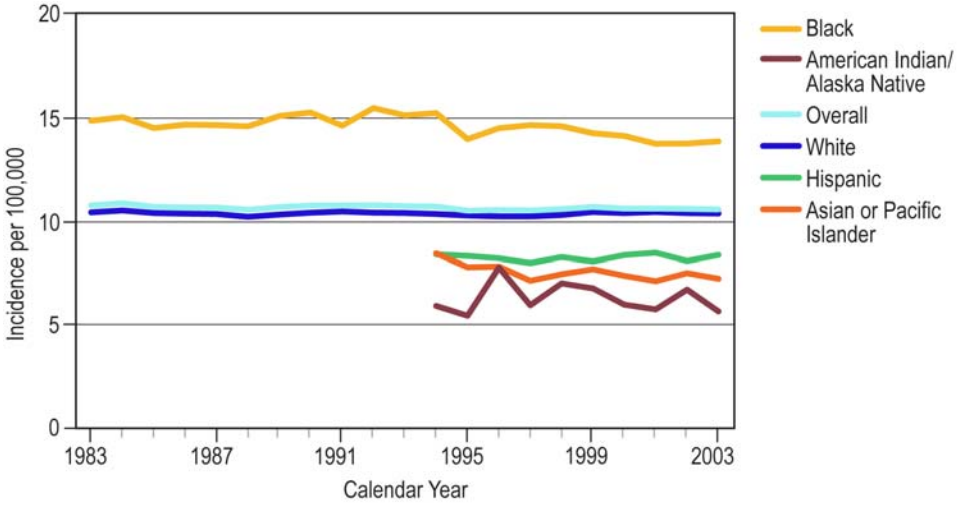


Figure 4. Pancreatic Cancer Mortality Rate Trends (All Races), 1983–2003
Source: NCI's Surveillance, Epidemiology, and End Results (SEER) Program

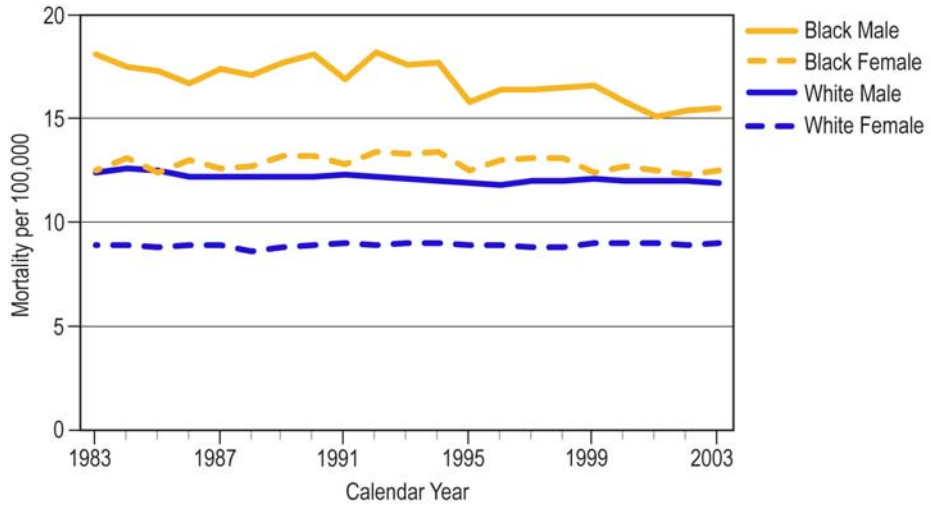


Figure 5. Pancreatic Cancer Male–Female Mortality Rate Trends, 1983–2003
Source: NCI's Surveillance, Epidemiology, and End Results (SEER) Program

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.*[1] 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, new models, and education and 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

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

NCI'S INVESTMENT IN PANCREATIC CANCER RESEARCH

This section describes NCI's progress toward addressing the 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 206%, from $21.8 million to $66.7 million. The largest increase (52%) occurred in FY2002, the year after the PRG report was published.

NCI's investment in pancreatic cancer-relevant research between FY2000 and FY2006[2] 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.

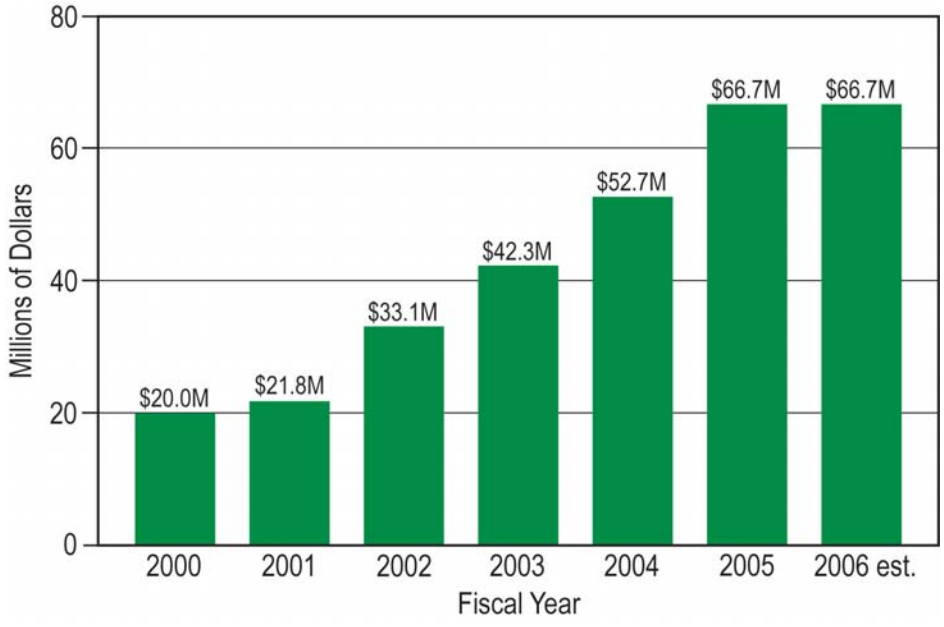


Figure 6. Trends in NCI Funding for Pancreatic Cancer Research, FY2000–FY2006

[2] FY2006 investment is estimated.

[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–FY2005

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%)
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2004	52.7	25 (141%)	4,724	3 (26%)
2005	66.7	27 (206%)	4,795	2 (28%)

[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 $17.3M in FY2005, an increase of 226%.

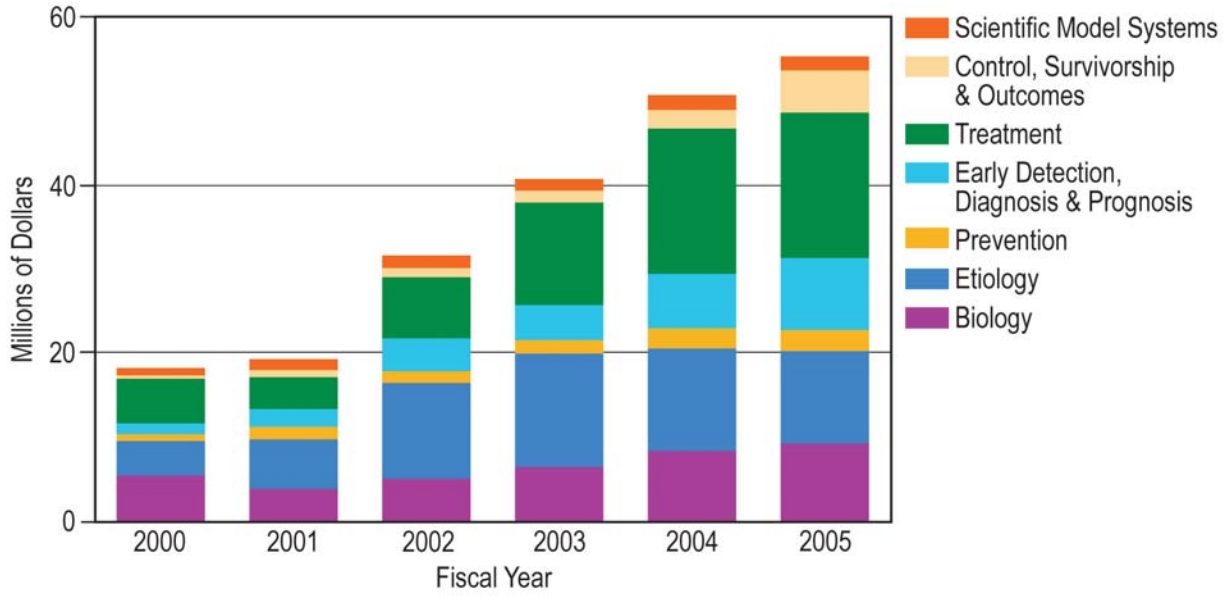

Figure 7. Dollar Estimates for Extramural Research by Scientific Area, FY2000–FY2005

[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 are included regardless of percent relevance to pancreatic cancer. Training grants are not included for FY2003–FY2004 because percent relevance was not assigned to training grants in those years.

Research Projects

Between FY2000 and FY2005, the number of NCI-sponsored research projects relevant to pancreatic cancer increased by 140%. The number of projects with 25% or greater pancreatic cancer relevance is shown in **Figure 8**.[5]

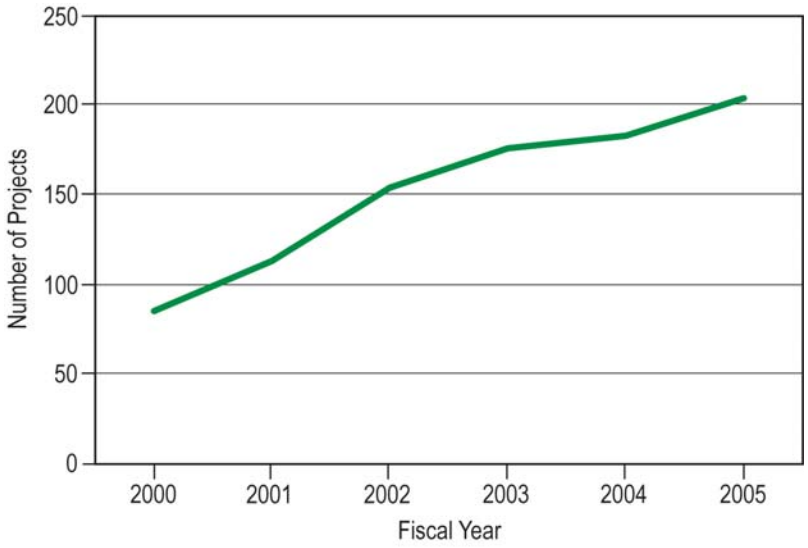

Figure 8. Total Number of NCI-sponsored Research Projects Relevant to Pancreatic Cancer, FY2000–FY2005

The funded portfolio of pancreatic research projects was classified according to the main PRG priority areas (**Figure 9**) and the specific recommendations in each priority area (**Figures 14**, **15**, **16**, **18**, and **19**). Several projects were relevant to more than one PRG recommendation category. In FY2005, the priority area with the highest number of relevant projects was risk, prevention, screening, and diagnosis, followed closely by tumor biology. Health services research had the smallest number of projects.

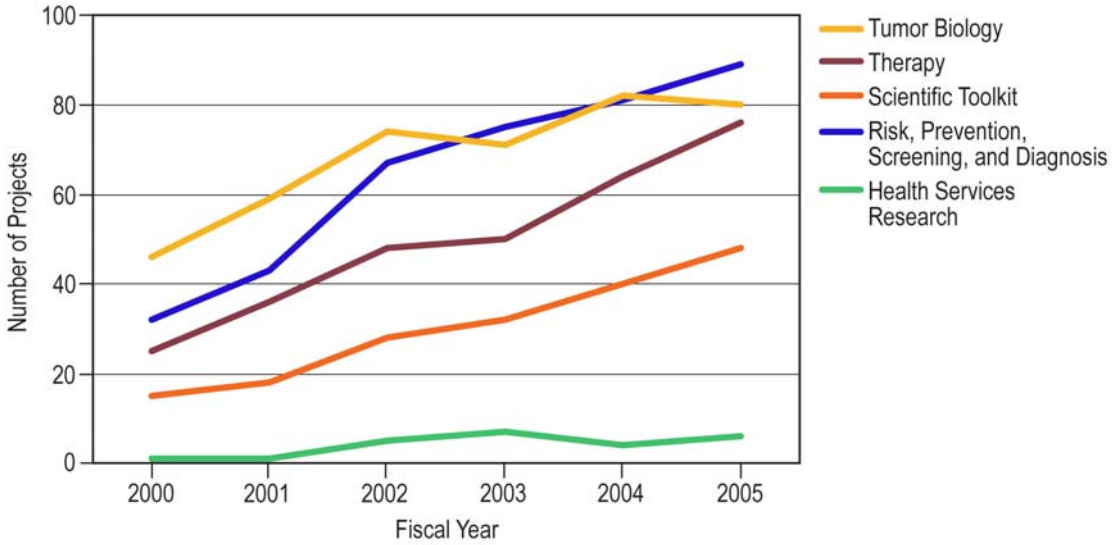

Figure 9. Pancreatic Cancer Research by PRG Category, FY2000–FY2005

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

Exception Funding

To address the PRG's call for increased funding for pancreatic cancer research, NCI implemented a new policy in FY2002 to increase 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. In FY2004 and FY2005, 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-FY2005. 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–FY2005

Source: NCI's Extramural Financial Data Branch

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
2005[a]	4	8	0
2004	3	3	2
2003	4	4	19
2002	3	3	17

[a] As of the writing of this report, data were not yet available on the number of R01s with 100% relevance to pancreatic cancer that were funded by NCI in FY2005 under its overall payline.

Clinical Trials

Between FY2000 and FY2005, NCI sponsored[6] 129 clinical trials relevant to pancreatic cancer. The number of active clinical trials each year by trial phase is shown in **Figure 10**.[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. NCI supported fewer than 15 studies in the "other" category (diagnostic studies and clinical studies addressing end-of-life issues) during this period.

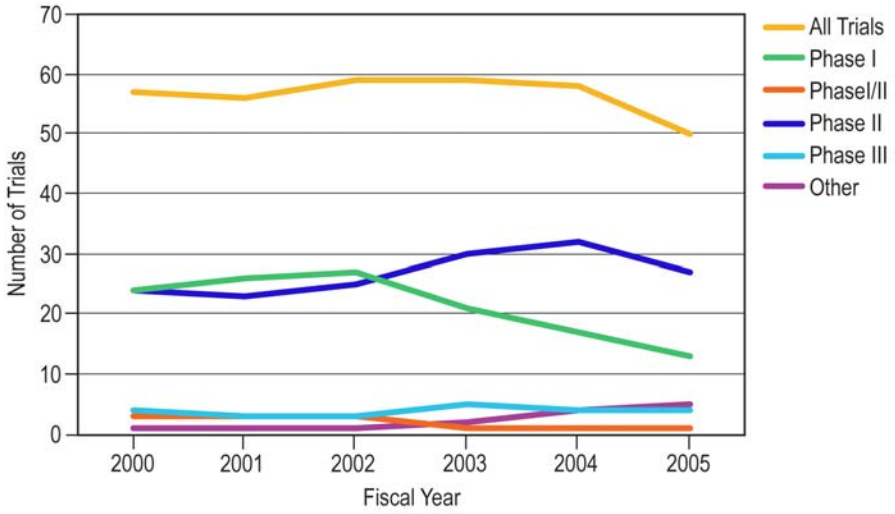

Figure 10. NCI-sponsored Pancreatic Cancer Clinical Trials Active during FY2000–FY2005

[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.

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 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 one P50 Specialized Center SPORE grant and two P20 Planning grants in pancreatic cancer 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**.

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-Epidermal Growth Factor Receptor (EGFR) Interactions in Pancreatic Cancer • Role of VAV1 Proto-Oncogene in Pancreatic Cancer
University of Alabama at Birmingham	Selwyn Vickers	P20 CA101955	• Gene Expression Profiling of Primary Pancreatic Tumor Cells • 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 • Development of New Generation CRAd for Pancreatic Cancer
University of Texas M.D. Anderson Cancer Center	James Abbruzzese	P20 CA101936	• Role of Endoplasmic Reticular (ER) Stress in Pancreatic Cancer Therapeutics • 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 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 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. Paula Kim, Co-Chair, Paula Kim Consulting
- Dr. James Abbruzzese, M.D. Anderson Cancer Center
- Dr. Ivan Ding, NCI
- Dr. Ralph Hruban, Johns Hopkins University
- 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 FY2005, the total number of investigators with NCI-funded R01 grants with greater than 25% relevance to pancreatic cancer increased from 34 to 82, representing a 141% increase. Several investigators had multiple R01 grants with varying levels of relevance to pancreatic cancer; thus, the total number of R01 grants for these years is greater than the number of investigators cited above. When all of the R01 grants were analyzed according to percent relevance to pancreatic cancer (**Figure 11**), the greatest increase was seen in those grants with the highest levels of relevance to pancreatic cancer (75%–100% relevant). Thus, for R01 pancreatic cancer grants, the number of unique principal investigators has grown substantially and this growth has been greatest in the projects that are most relevant to pancreatic cancer.

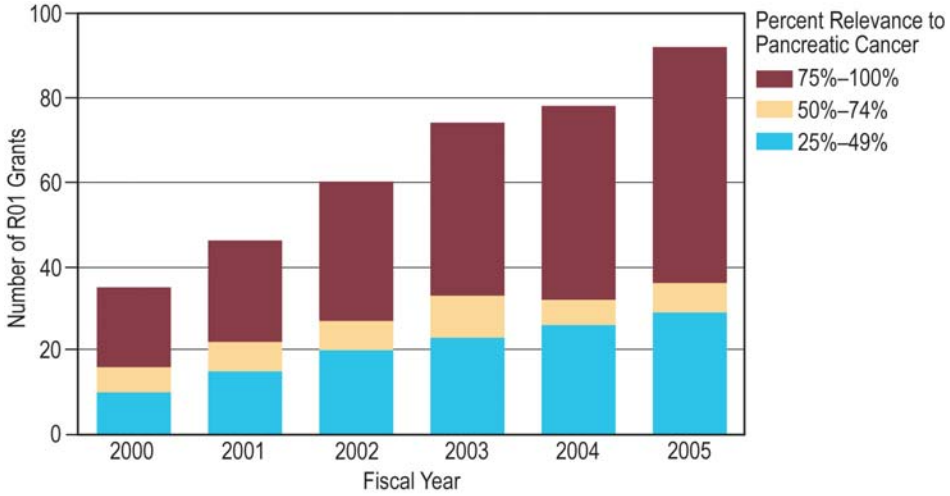

Figure 11. Number of R01 Grants by Relevance to Pancreatic Cancer, FY2000–FY2005
Note: Grants with less than 25% relevance were not included in this analysis.

Training

Grant mechanisms used by NCI for pancreatic cancer research training include F31, F32, K01, K07, K08, K22, K24, 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. In FY2006, an estimated 31 distinct training projects were relevant to pancreatic cancer research and approximately $2.7 million was spent on these projects.[8]

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

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 248 between calendar years 2000 and 2005 (**Figure 13**), representing an 81% increase. These values derive from a search of the MEDLINE database[10] 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.

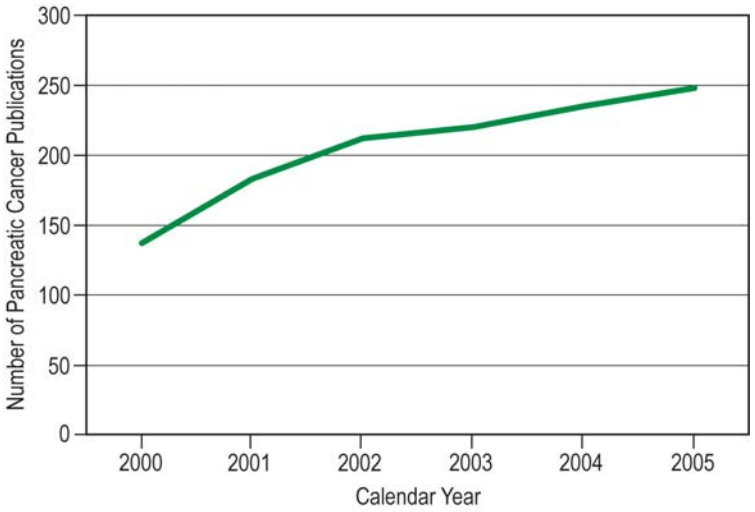

Figure 13. Estimated Number of Scientific Articles on Pancreatic Cancer Research Acknowledging NCI Support, 2000–2005

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

Research Institutions

Currently, 77 research institutions across the United States and 1 overseas institution receive NCI funding for pancreatic cancer research.[9] The geographic breakdown of U.S. institutions that received NCI funds for pancreatic cancer research in FY2005 (25% or greater relevance to pancreatic cancer) is shown in **Figure 12**. California, Massachusetts, Pennsylvania, Texas, New York, and Alabama have the highest numbers of institutions with NCI-funded pancreatic cancer research grants.

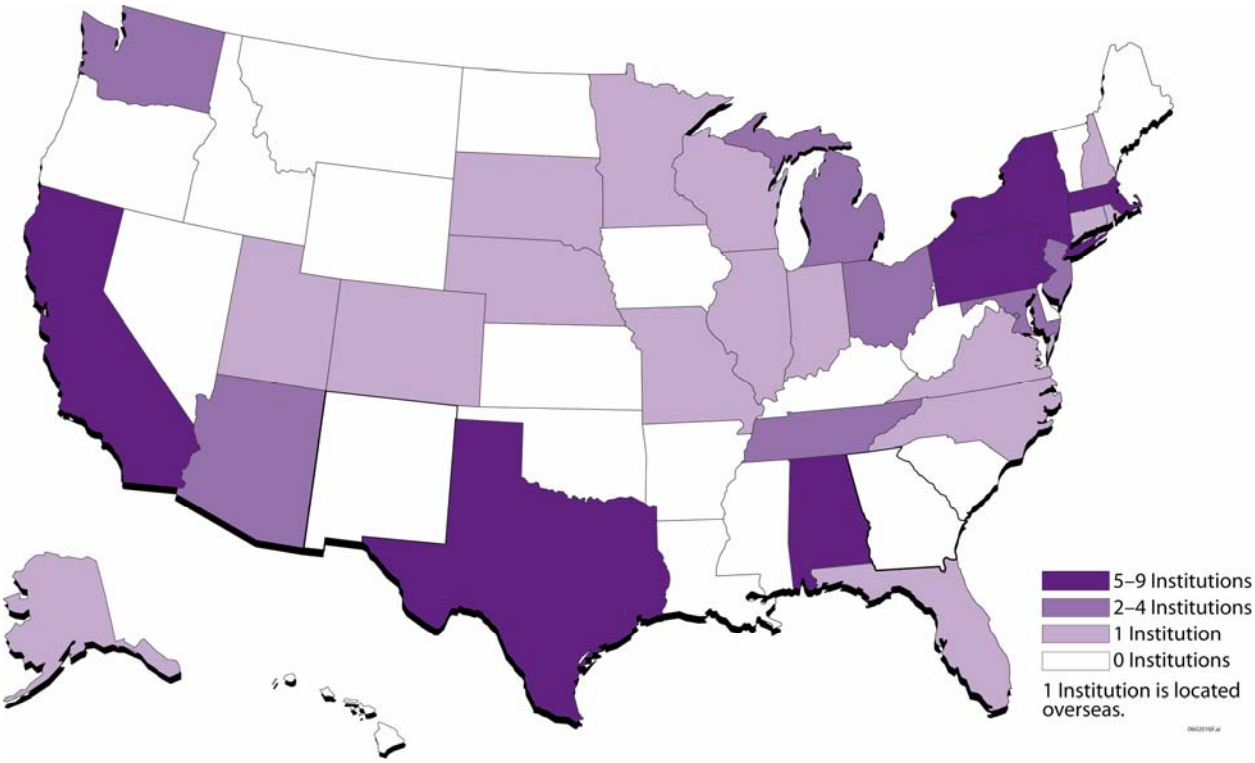

Figure 12. Distribution of NCI-funded Institutions Conducting Pancreatic Cancer Research in FY2005

[9] Includes research funded in FY2005 that was at least 25% relevant to pancreatic cancer, as well as training and intramural projects.

Research Projects

The majority of pancreatic cancer projects relevant to tumor biology addressed the development of pancreatic adenocarcinoma (**Figure 14**). Between FY2000 and FY2005, there was an increase in the number of projects relevant to each of the PRG recommendations in the area of tumor biology.

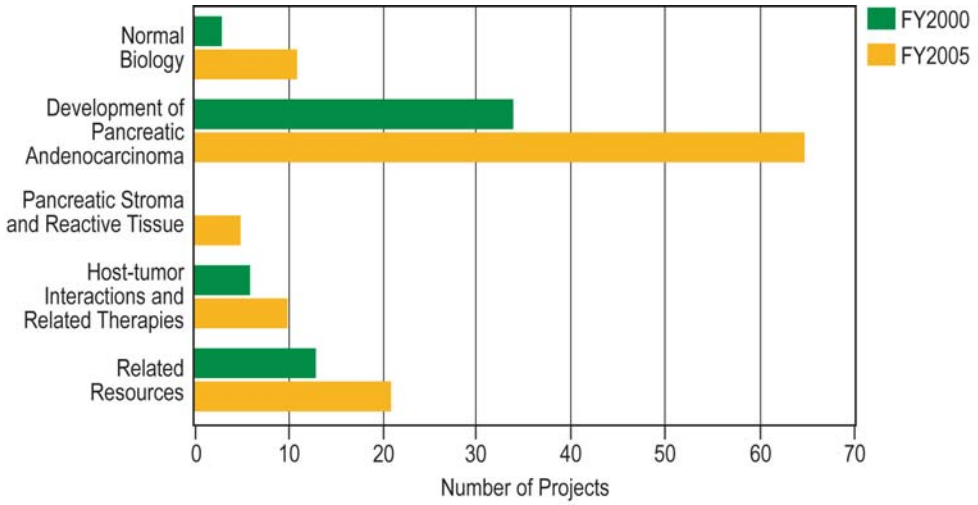

Figure 14. Pancreatic Cancer Projects Related to Tumor Biology, FY2000 and FY2005

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:

- **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.
- **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 one pancreatic cancer study.
- **Ubiquitin and Ubiquitin-like Modifications Regulating Disease Processes**—Supports studies of the roles of ubiquitin and ubiquitin-like 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 of Aging.
  - This PA was issued in 2006 and previously released versions of the current initiative have funded one pancreatic cancer study.

- **Pilot Studies in Pancreatic Cancer**—Promotes innovative multidisciplinary research to better understand the biology, etiology, detection, prevention, and treatment of pancreatic cancer.
  - This PA was issued in 2006 and has not yet funded any studies.

Research Highlights

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

- Cyclin D1 Protein in Pancreatic Cancer Drug Resistance. Pancreatic cancer is invariably 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.[11]
- Gene-Associated Pancreatic Cancer Risk. The Pancreatic Cancer SPORE at the Mayo Clinic is nearing completion of gene analyses previously reported in the scientific literature to have some association with pancreatic cancer. Findings indicate that most of these genes do not contribute significantly to the risk of pancreatic cancer; however, other genes suggest very strong associations.
- Potential New Targets for Controlling Pancreatic Cancer Progression and Metastasis. The Mayo Clinic Pancreatic Cancer SPORE also is exploring a new pathway involving the interaction of the chemokine (small secreted protein signal) SDF-1 alpha and its receptor CXCR4 with the EGFR. Findings indicate that these are promising targets for modulating growth, blood vessel formation, and metastasis in human cancers, including pancreatic cancer.

[11] 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.

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 15**). The number of projects related to each PRG recommendation in this area increased between FY2000 and FY2005.

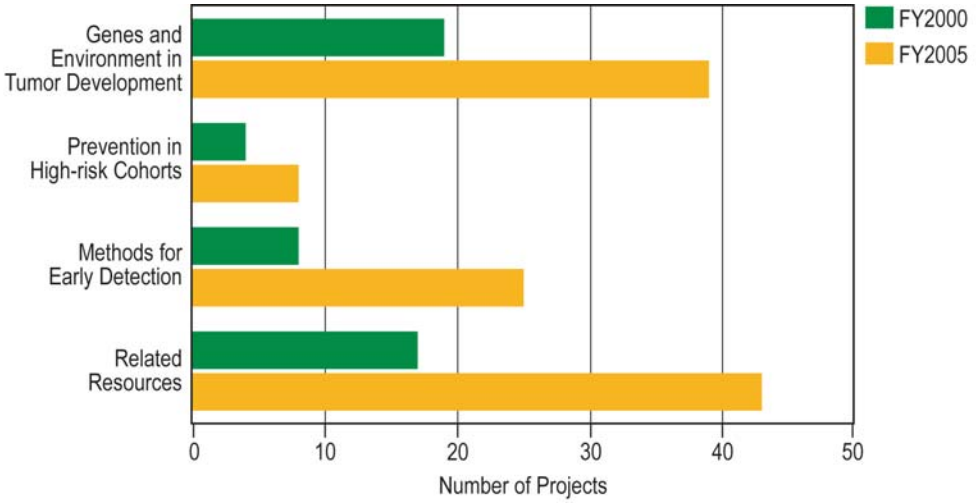

Figure 15. Pancreatic Cancer Projects Related to Risk, Prevention, Screening, and Diagnosis, FY2000 and FY2005

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 and 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 or are related to pancreatic cancer but are too new to have funded any projects at the time this report was written:

- **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 2004 and has funded four pancreatic cancer studies.
- **Small Grants Program for Cancer Epidemiology**—Provides support for small projects focused on cancer etiology that may lead to cancer control/prevention.
  - This PA reviewed in an NIH Institute (PAR) was issued in 2006; previous versions funded three pancreatic cancer studies.

- **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 2005 and has not yet funded any projects.

Research Highlights

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

- Diabetes Link to Pancreatic Cancer Development. Men who report having diabetes and taking medication for it have more than two and a half times the risk of developing pancreatic cancer compared to men without diabetes. The next step for the researchers is to define the biological mechanisms by which diabetes may cause cancer.[12]
- Pancreatic Cancer Risk Association with Non-Cigarette Tobacco Products. Cigarettes are not the only form of tobacco that may be associated with pancreatic 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.[13]
- 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. The SPORE's patient registry will help to characterize and elucidate the epidemiological and genetic basis for this clustering. The studies have been and are being translated to better patient care in the forms of better genetic counseling and screening for early noninvasive precancerous tumors in the pancreas.
- Pancreatic Risk Factors in Older Male Smokers. Analyses of data from 27,111 male smokers ages 50–69 years enrolled in the Alpha-Tocopherol, Beta-Carotene Prevention Study[14,15,16] in Finland yielded the following findings:
  - 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.
  - Higher levels of physical activity and lower intake of carbohydrates are associated with a reduced risk of pancreatic cancer in male smokers; the reverse is also true.

[12] Details available in NCI Cancer Bulletin 2004, Oct 26; 1(41):3.
[13] 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.
[14] Published in Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. A prospective study of medical conditions, anthropometry, physical activity, and pancreatic cancer in male smokers (Finland). *Cancer Causes Contro*l. 2002 Jun;13(5):417-26.
[15] Published in Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. Prospective study of diet and pancreatic cancer in male smokers. *Am J Epidemiol*. 2002 May 1;155(9):783-92.
[16] Published in Stolzenberg-Solomon RZ, Graubard BI, Chari S, Limburg P, Taylor PR, Virtamo J, Albanes D. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. *JAMA*. 2005 Dec 14;294(22):2872-8.

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 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.[17]

[17] 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.

Research Projects

The majority of projects related to pancreatic cancer therapy focus on the discovery and development of targeted therapeutics (**Figure 16**). The total number of projects in this category more than doubled from FY2000 to FY2005 due to increases in the numbers of projects relevant to each of the therapy-related PRG recommendations.

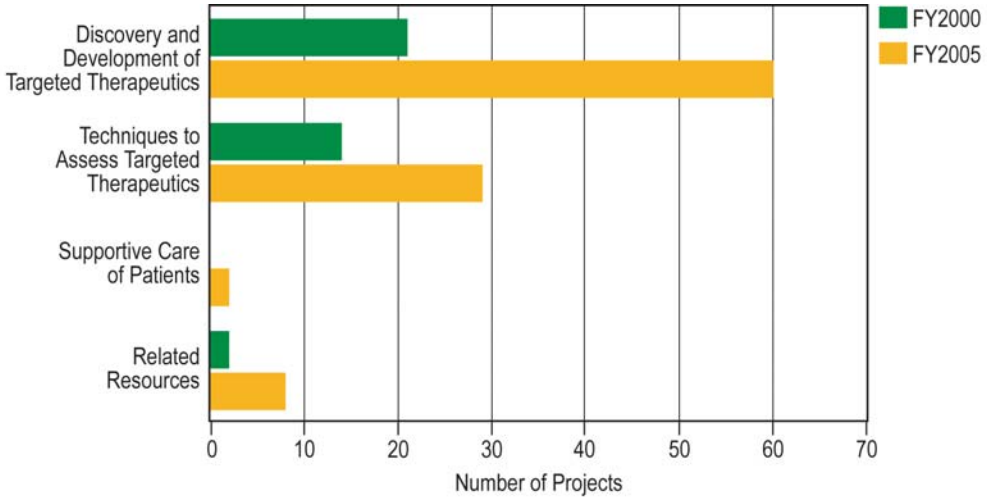

Figure 16. Pancreatic Cancer Projects Related to Therapy, FY2000 and FY2005

Clinical Trials

The number of NCI-sponsored clinical trials related to pancreatic cancer therapy (**Figure 17**) increased slightly in 2002, the year that the Pancreatic Cancer PRG report was published, and has remained relatively stable since then. NCI sponsors many more trials related to treatment than to supportive care.[18]

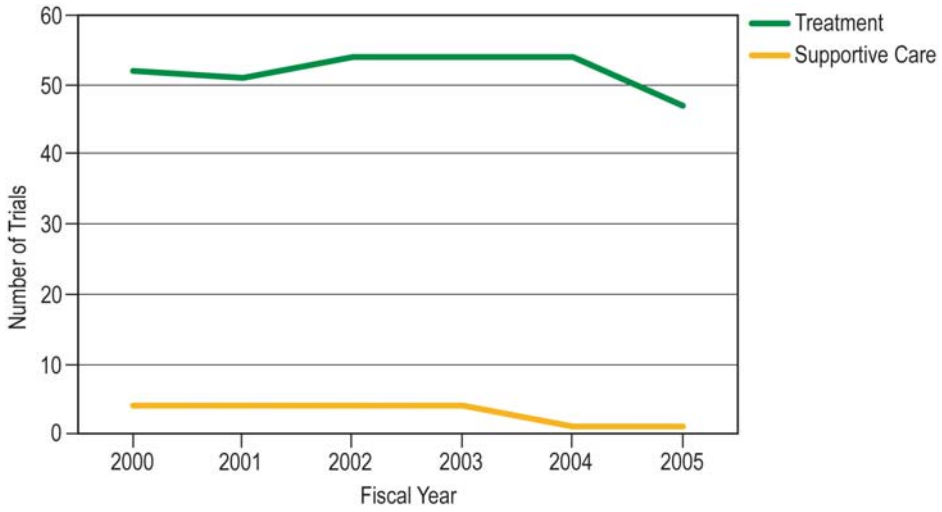

Figure 17. Pancreatic Cancer Clinical Trials Related to Therapy, FY2000–FY2005

Several ongoing NCI-sponsored clinical trials are evaluating novel agents and 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 are large randomized trials, involve new chemotherapeutic and biologic agents, and accrue participants 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. Results from these trials should be available in 2006 and 2007.

- ***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.
- ***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.
- ***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

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

patients with advanced or metastatic pancreatic cancer. This trial enrolled approximately 590 patients between 2004 and 2006.

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 or are related to pancreatic cancer but are too new to have funded any projects at the time this report was written:

- **Rapid Access to Intervention Development (RAID)**—Efficiently moves novel treatment interventions developed in academic settings into the clinic.
  - Two 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.
  - This PA was issued in 2006 and previously released versions of this initiative have funded three pancreatic cancer studies.

Research Highlights

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

- Refinement of COX-2 Inhibitor Use in Pancreatic Cancer. COX-2 inhibitors appear to be able to promote as well as inhibit pancreatic tumor growth and blood vessel formation. These findings suggest that certain pancreatic cancer patients may respond differently to selective COX-2 inhibitors and that use of these drugs should be based on the tumor's COX-2 expression profile.[19]
- 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.[20] 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.
- 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

[19] Details available in NCI Cancer Bulletin 2004, Apr 6; 1(14): 5.
[20] Details available in Erlotinib Plus Gemcitabine Boosts One-Year Survival in Pancreatic Cancer, Clinical Trial Results, cancer.gov.

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.

- 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.[21]

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

Research Projects

Although a smaller number of pancreatic cancer projects are related to health services research (**Figure 18**) than any of the other PRG priority areas, the number of projects related to this group of recommendations increased between FY2000 and FY2005. [22]

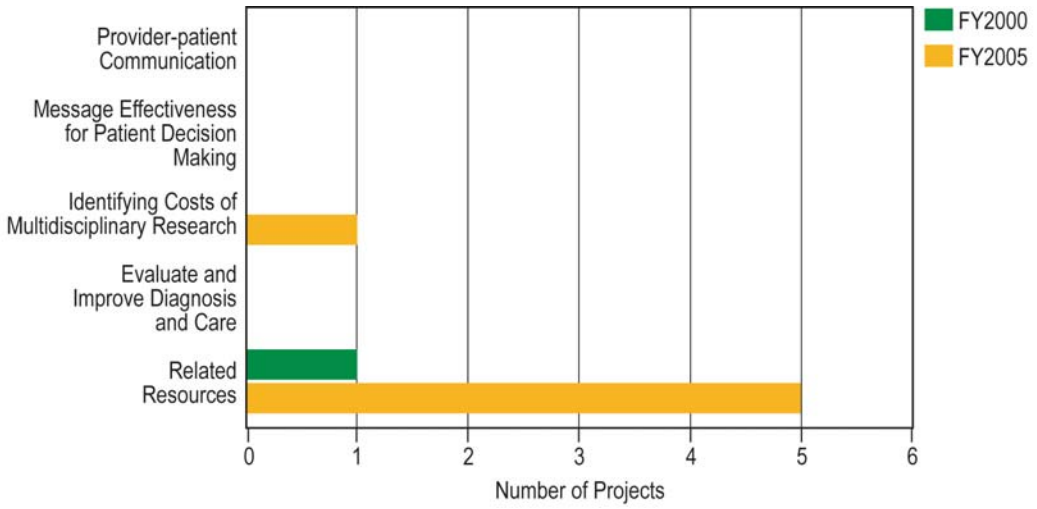

Figure 18. Pancreatic Cancer Projects Related to Health Services Research, FY2000 and FY2005

Initiatives

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

- **Small Grants Program for Behavioral Research in Cancer Control**—Issued in 2006, this PAR (and previously released versions of this PAR) solicits research on cancer control topics, including health communications and patient decision making; at least one pancreatic cancer study has been funded.

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

Research Projects

The number of projects related to the pancreatic cancer scientific toolkit increased substantially between FY2000 and FY2005 (**Figure 19**), with increases for each of the PRG recommendations in this priority area except for organization of signal transduction knowledge.

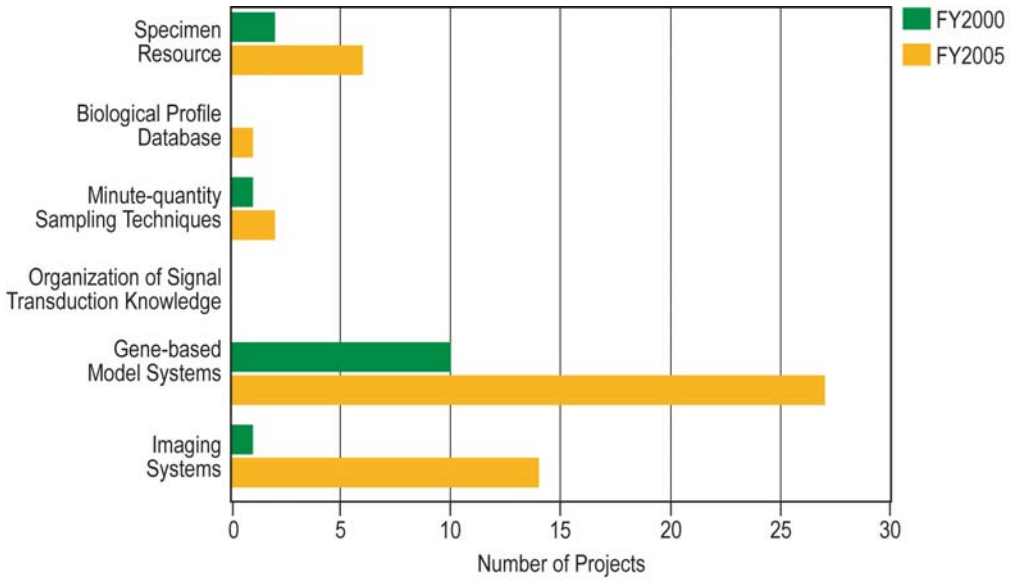

Figure 19. Pancreatic Cancer Projects Related to Scientific Toolkit, FY2000 and FY2005

Initiatives

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

- **Mouse Models of Human Cancers Consortium**—Has supported several studies of mouse models that may provide insight into pancreatic cancer in humans.
  - This RFA was issued in 2002 and has funded four pancreatic cancer projects.
- **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, issued in 2006, and previous versions funded three pancreatic cancer projects.

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.[23]
- 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.[24]
- BRCA2-Deficient Mouse Model to Support Novel Therapy Studies. A study focusing on the molecular mechanisms underlying the function of the BRCA2 gene as a tumor suppressor in pancreatic cancer has led to novel methods for killing BRCA2 mutant cells. SPORE investigators are generating a pancreatic-specific BRCA2-deficient mouse model to test novel therapies for treating pancreatic cancer resulting from genetic defects.
- Cell Line Adaptation Restoring Smad4 Signaling to Test Treatment Sensitivity. Investigators at the University of Alabama at Birmingham are adapting a cell line and an *in vitro* model to test whether restoration of signaling of *Smad4*, a tumor-suppressor gene, creates cells that are more sensitive to treatment.

[23] 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.

[24] 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 PRG. 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 50 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.