Chapter 1:
Breast Cancer Research, 1998-2003

By applying and expanding our foundation of knowledge, and with ample measures of teamwork, technology, and tenacity, major progress against breast cancer can and will be made in the next 5 to 10 years. *Charting the Course: Priorities for Breast Cancer Research*

Breast cancer is the most common non-skin cancer in women and the second most common cause of cancer-related death in U.S. women.[1] An estimated 215,000 new breast cancer diagnoses and 40,000 breast cancer deaths are expected in 2004.[2]

As shown in Figure 1-1, breast cancer incidence rates increased steadily between 1973 and the late 1990s, following the increased use of mammography.[3] After peaking in 1998, incidence has declined slightly. White women have a higher incidence of breast cancer than any other race, and African-American women have the second highest incidence rates. Incidence rates for whites and African Americans have increased similarly over the past three decades.

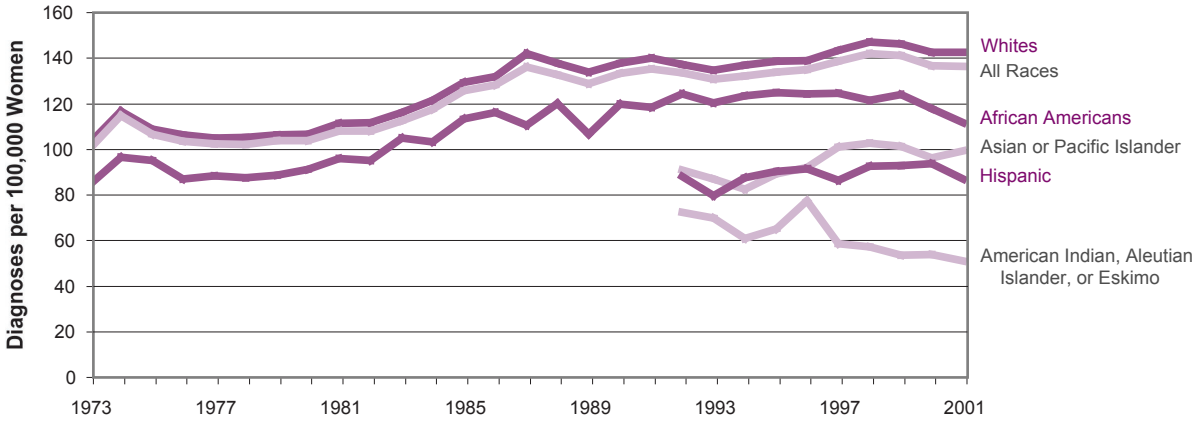

Figure 1-1. Breast cancer incidence in the United States
Data derived from NCI's SEER Program

Overall mortality rates were stable between 1973 and the early 1990s,[4] and then began a steady decline that has continued throughout the last decade (Figure 1-2, page 2). In 2001, mortality rates were lower than at any time since 1973, when SEER began collecting these data. The most recent mortality rates represent an impressive decrease of approximately 20% from the rates in the 1980s. However, while mortality rates in white women were stable until the early 1990s and then began declining, mortality rates for African-American women increased steadily through the 1980s, surpassing the rates for white women and all races combined in that decade. Mortality rates for African-American women began to decline in the mid-1990s, although they are still about 35% higher than rates for white women.

1 NCI's Surveillance, Epidemiology, and End Results (SEER) *Cancer Statistics Review, 1975-2001*.

2 See Note 1.

3 The first year in which incidence and mortality data were collected by the NCI's SEER program for all races, whites, and blacks, was 1973. Beginning in 1992, the data collected were expanded to include additional racial/ethnic groups. The most recent year for which analyzed SEER data are available is 2001.

4 See Note 1.

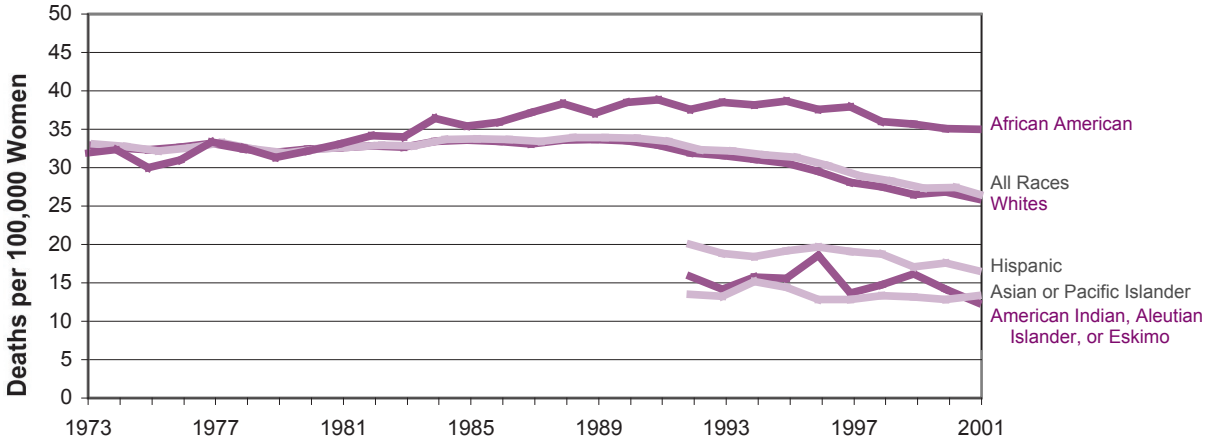

Figure 1-2. Breast cancer mortality in the United States

Breast cancer is associated with a large economic toll in addition to premature death, disability, and treatment sequelae, including quality-of-life issues. It is estimated that $5.4 billion is spent in the United States each year on treatment of the disease.[5] Lost productivity and wages are additional burdens.

The Breast Cancer Progress Review Group

In September 1997, the National Cancer Institute (NCI) convened a multidisciplinary committee of scientists, clinicians, and advocates to review the field of breast cancer research and make prioritized recommendations concerning the most needed and promising directions for future NCI investment. In August 1998, this Breast Cancer Progress Review Group (PRG) issued its report *Charting the Course: Priorities for Breast Cancer Research*, which addressed eight categories of breast cancer research: Biology; Etiology; Genetics; Prevention; Early Detection, Diagnosis, and Prognosis; Treatment; Cancer Control; and Outcomes. For each research category, the report included a synopsis of current knowledge, a discussion of identified goals, barriers to progress, and key scientific questions and opportunities, accompanied by recommended actions.[6]

The Breast Cancer PRG was one of two PRGs formed in 1997. The Breast Cancer PRG was composed of 30 nationally prominent members from academia, industry, nonprofit organizations, and government, with complementary backgrounds in basic, translational, and clinical research and in breast cancer advocacy issues. The objectives of the Breast Cancer PRG were to review the state of the science, assess the existing NCI breast cancer research portfolio, identify and prioritize key scientific questions, and develop recommendations for action. The expertise of the PRG members was complemented by 200 additional scientists, clinicians, and advocates who participated in a roundtable meeting.

Since the Breast Cancer PRG issued its report, the NCI has increased its investment in research relevant to breast cancer in terms of dollars spent and the number of projects supported. Numerous resources and programs have been sustained, expanded, and/or developed. During this time, the NCI has improved the monitoring of basic and clinical research to better track progress and plan future goals. The Institute has also enhanced early detection methods, developed novel treatments, identified new prevention mechanisms, and improved our understanding of genetic predisposition. Ultimately, these accomplishments have helped reduce mortality from breast cancer.

5 In 1996 dollars, as determined by Brown, Riley, and Etzioni and reported in the NCI's *Cancer Progress Report—2003 Update*.

6 The Breast Cancer PRG report identified 64 investigative priorities; three of these priorities were further divided into 28 subpriorities. Accompanying the 64 investigative priorities were 163 recommended actions. Although the PRG report included 64 investigative priorities, some had overlapping content. For reporting purposes, the NCI has combined selected priorities' overlapping content, as described in the appropriate chapters.

Peer-reviewed publications resulting from NCI-sponsored efforts show that much progress has been made in specific topic areas identified as promising by the PRG. Further demonstration of progress can be found in breast cancer-related patents that have been issued and changes in clinical practice that have been adopted.

In 2004, the NCI established an internal Breast Cancer Working Group to assist in planning, monitoring, and tracking progress in addressing the recommendations of the Breast Cancer PRG. This report includes the Breast Cancer Working Group's findings regarding the NCI's responsiveness to the PRG recommendations during the years 1998 through 2003.

Six Years of Progress

In the years that followed the release of the Breast Cancer PRG report, the number of investigator-initiated research projects relevant to breast cancer increased, and specific research initiatives were implemented or expanded. In the sections that follow, an overview is provided for the following:

- The NCI's investment in breast cancer research, in terms of dollars invested; research projects supported; clinical trials supported; initiatives undertaken; and resources developed, maintained, and expanded.
- The return on NCI's investment in terms of research results obtained and applied.

Investment in Breast Cancer Research

Dollars Invested

NCI's commitment to addressing the identified challenges and opportunities in breast cancer research is demonstrated by growing investments in relevant activities. Figure 1-3 shows dollar estimates for NCI breast cancer spending from fiscal year (FY) 1998 through FY2003. Over the 6 year period, NCI's overall breast cancer investment increased by almost 60%. For each of these years, NCI's support for breast cancer research was greater than that for any other cancer site.

Values include NCI's total intramural and extramural support for breast cancer research as reported by the Financial Management Branch of the NCI's Office of Budget and Financial Management (NCI FactBook).

The majority of funds devoted to breast cancer research supported the extramural research program. Figure 1-4 (page 4) shows the NCI's dollar investment for breast cancer-relevant research during FY1998-2003. This information is broken down according to the Common Scientific Outline (CSO), a classification system created to provide a common approach to comparing and assessing cancer research that is supported by different funding organizations.[7]

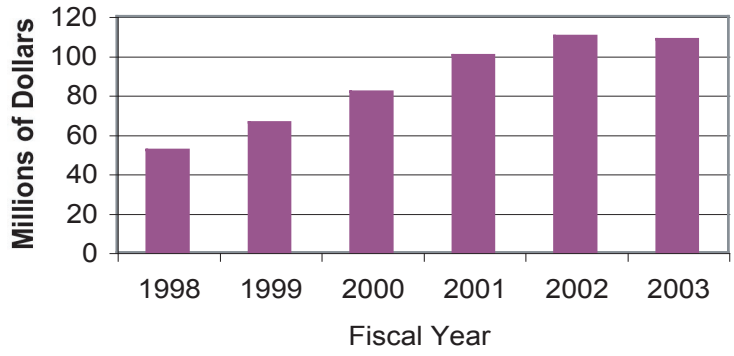

Figure 1-3. Estimate of total NCI dollars for breast cancer-relevant research

To derive the values for extramural research, dollars associated with each funded project were first prorated by estimated breast cancer relevance, and this portion was then equally distributed among applicable CSO research categories. Dollars directed at resources are included in the values for the research categories.

7 Although the seven categories of the CSO are similar to the eight categories of the Breast Cancer PRG, notable differences include the CSO's category of scientific model systems; the combined category of cancer control, survivorship, and outcomes; and the inclusion of genetics in the other categories. The CSO is described in its entirety at http://researchportfolio.cancer.gov/cso.html.

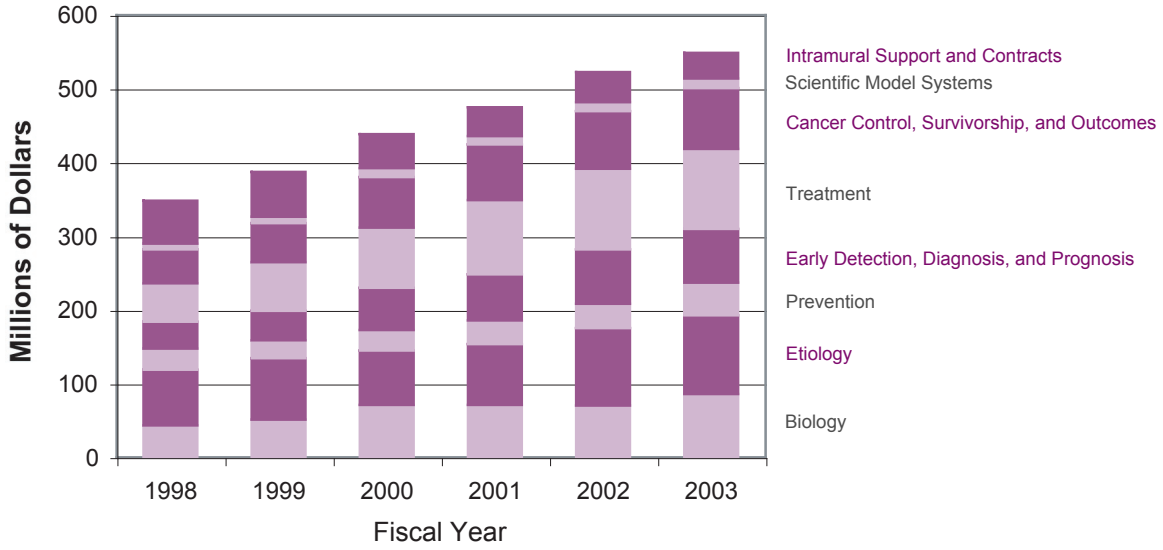

Figure 1-4. Dollar estimates for breast cancer-relevant research by type of research

Research Projects Supported

Between 1998 and 2003, the number of NCI-sponsored research projects relevant to breast cancer increased by 60%. Figure 1-5 shows the number of projects with breast cancer relevance[8] (i.e., 25% or greater) that were funded by the NCI each year during FY1998-2003. Numbers of funded breast cancer projects within each research category are shown in Figure 1-6 (page 5). Details concerning the NCI-sponsored research projects in each category can be found in Chapters 3 through 8 and Appendix B[9].

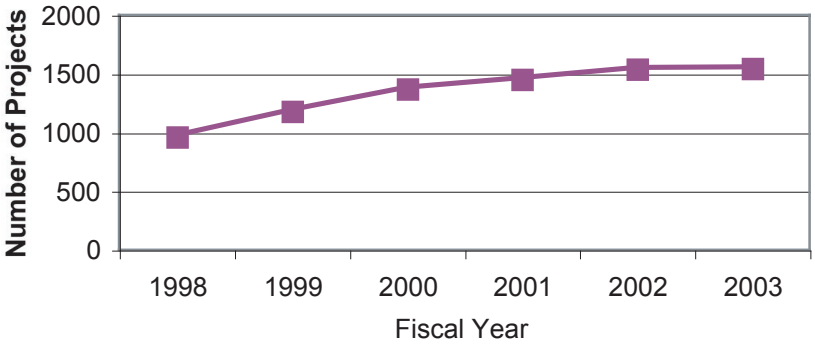

Figure 1-5. Number of research projects relevant to breast cancer

Included in the graph are solicited and unsolicited projects and individual training and career development awards, both new and continuing, with breast cancer relevance values of 25% of more. (Solicited projects are those resulting from submissions in response to NCI initiatives in targeted topic areas; unsolicited projects are those resulting from the other submissions received by the NCI.)

Each project with 25% or greater relevance to breast cancer was counted once for each category to which it applied.[10]

8 Quantitative estimates of cancer-site relevance are made by NCI staff based on the proportion relevant to disease sites. The NCI uses relevance values for calculating prorated dollar allocations (as in Figure 1-3) and for project tracking.

9 Appendix B identifies the FY2003 research projects that were responsive to the PRG priorities.

10 Category assignment was based on the results of mapping projects to the 64 PRG recommendations and not on original CSO assignments. Projects that are assigned to more than one research category are included in the data for all appropriate categories.

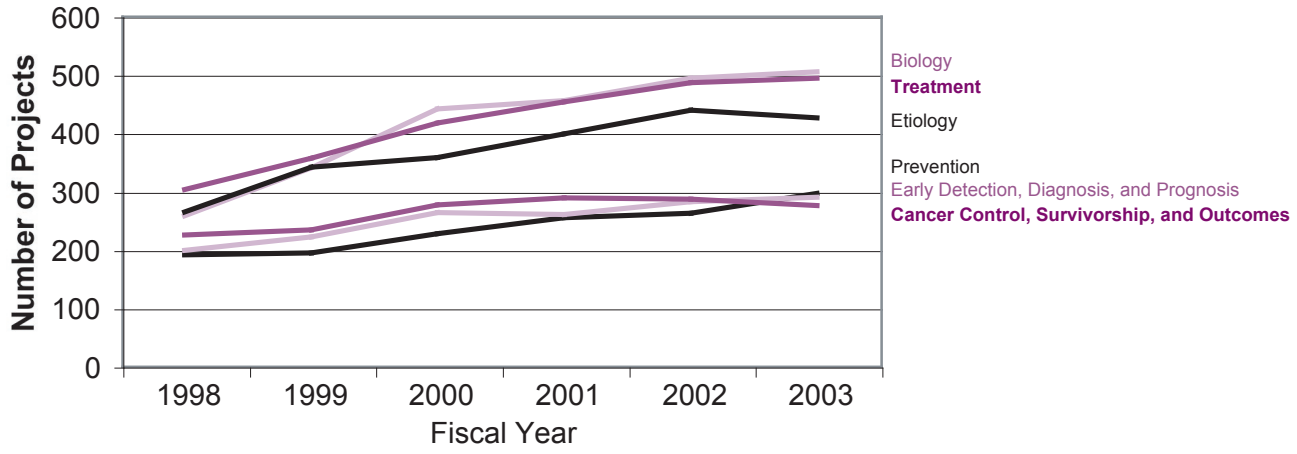

Figure 1-6. Number of breast cancer-relevant projects addressing each research category

Clinical Trials Supported

Between 1998 and 2003, the number of active NCI-sponsored clinical trials relevant to breast cancer increased. Figure 1-7 shows the increase in the overall number of NCI-sponsored[11] clinical trials relevant to breast cancer that were active during the calendar years 1998 to 2003. These clinical trials represent research on treatment, prevention, genetics, diagnostics, and supportive care.

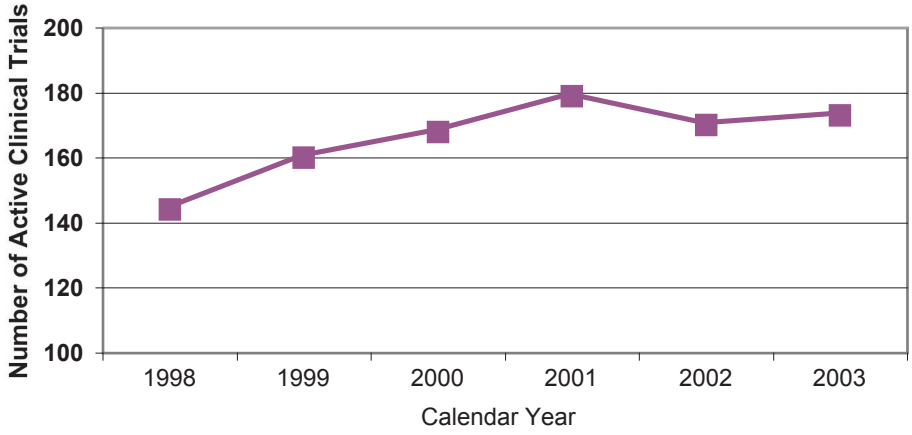

Figure 1-7. Number of NCI-sponsored breast cancer clinical trials active during calendar years 1998-2003

These data indicate overall numbers of breast cancer clinical trials. (Information in the figure is based on a search conducted by staff of the Office of Cancer Information Products and Systems, Office of Communications [in its PDQ Clinical Trials Database] for NCI-sponsored breast cancer treatment trials active at some time during the timeframe 1998 to 2003.) More detailed information about specific trials is available on NCI's Cancer.gov website at http://www.cancer.gov/clinical_trials.

Initiatives Undertaken

Between FY1998 and FY2003, numerous NCI initiatives supported work on the research priorities identified by the Breast Cancer PRG. The initiatives increased the depth and breadth of the NCI's research on breast cancer by:

- Encouraging submission of applications for research projects that are wholly or partially focused on breast cancer in targeted topic areas
- Developing and maintaining resources for use by breast cancer researchers
- Establishing and expanding programs in which research and resources are combined in collaborative pursuit of a common goal

11 An NCI-sponsored clinical trial in the Physician Data Query (PDQ): (1) has been reviewed and approved by NCI's CTEP Protocol Review Committee or by an approved NCI-designated Cancer Center Protocol Review and Monitoring System, and/or (2) receives support through an NCI grant or cooperative agreement.

Table 1-1 lists the NCI initiatives that resulted in breast cancer research in FY1998 through 2003[12] and identifies the chapter of this report in which more detail on the initiatives is provided.

Table 1-1. NCI Initiatives Relevant to Breast Cancer Research: 1998-2003

Initiatives Focused on Breast Cancer

Chapter 2: General Initiatives

- Aging Women and Breast Cancer: PA-00-001 (continued in FY2000)
- Breast and Ovarian Cancer Family Registries (CFRs): http://epi.grants.cancer.gov/BCFR/index.html (ongoing)
- Breast Cancer Faculty: http://ccr.cancer.gov/faculties/faculty.asp?facid=129 (ongoing)
- Breast Cancer Surveillance Consortium (BCSC): http://breastscreening.cancer.gov/ (ongoing)
- Cooperative Breast Cancer Tissue Resource (CBCTR): http://www-cbctr.ims.nci.nih.gov/ (ongoing)
- Insight Awards to Stamp Out Breast Cancer: PAR-99-128 (begun in 1999)
- International Breast Cancer Screening Network (IBSN): http://appliedresearch.cancer.gov/ibsn/ (begun FY1998)
- Specialized Programs of Research Excellence (SPOREs) in Breast Cancer: http://spores.nci.nih.gov/breast/breast.html (ongoing)

Chapter 3: Biology

- Stages of Breast Development: Normal to Metastatic Disease: PA-99-162 (begun in 1999)

Chapter 4: Etiology

- Breast Cancer and the Environment Research Centers: RFA-ES-03-001 (begun in 2003)
- Long Island Breast Cancer Study Project: http://epi.grants.cancer.gov/LIBCSP/Overview.html (ongoing)
- Regional Variation in Breast Cancer Rates in the U.S.: RFA-CA-98-017 (begun in 1998)

Chapter 5: Prevention

- Chemoprevention of Estrogen Receptor-Negative Breast Cancer Preclinical Studies: RFA-CA-03-005 (begun in FY2002)
- Study of Tamoxifen and Raloxifene (STAR) Trial: http://www.cancer.gov/star (begun in FY1999)

Chapter 6: Early Detection, Diagnosis, and Prognosis

- Development of Digital Mammography Displays and Workstations: PA-99-082 and PA-99-083 (begun in 1999)

Initiatives With Breast Cancer-Relevant Components

Chapter 2: General Initiatives

- Applications of Innovative Technologies for the Molecular Analysis of Cancer: PAR-01-106 and PAR-01-107 (begun in FY1999; continued in FY2001)

12 Initiatives selected for inclusion are those that were begun or continued during FY1998-2003 that resulted in programs, resources, or research projects relevant to breast cancer. Also selected for inclusion are ongoing NCI intramural initiatives that have a readily identifiable component that is specific to breast cancer.

- Basic and Preclinical Research on Complementary and Alternative Medicine (CAM): PA-02-124 (begun FY2002)
- Bioengineering Research Grants: PA-02-011 (begun FY1999)
- Bioengineering Research Partnerships: PAR-03-032 (begun in FY1999)
- Cancer Biomedical Informatics Grid (caBIG): http://cabig.nci.nih.gov/ (begun in FY2003)
- Cancer Centers Program: www3.cancer.gov/cancercenters/ (ongoing)
- Cancer Genetics Services Directory: http://www.cancer.gov/search/genetics_services/
- Cancer Genome Anatomy Project (CGAP): http://cgap.nci.nih.gov/ (ongoing)
- Cancer Imaging Program (CIP): http://www3.cancer.gov/dip (ongoing)
- Cancer Molecular Analysis Project (CMAP): http://cmap.nci.nih.gov (ongoing)
- Cancer Prognosis and Prediction: PAR-03-098 and PAR-03-099 (begun in FY2001; continued in FY2003)
- Cancer Research Network (CRN): http://cancercontrol.cancer.gov/bb/can_research.html (begun in FY1998)
- Cancer Research Small Grant Program: PAR-02-176 (ongoing; reissue of the Cancer Prevention Research Small Grant Program)
- Cancer Research Training, Career Development and Education Opportunities: http://cancertraining.nci.nih.gov/ (ongoing)
- Clinical Trials Cooperative Group Program: http://ctep.cancer.gov/resources/coop2.html (ongoing)
- Community Clinical Oncology Program (CCOP): http://www3.cancer.gov/prevention/ccop (ongoing)
- Competing Supplements for Organotypic Models of Cancer: PAR-02-052 (begun in FY2002)
- Cooperative Human Tissue Network (CHTN): http://www-chtn.ims.nci.nih.gov/ (ongoing)
- Correlative Studies Using Specimens from Multi-institutional Treatment Trials: PA-03-064 (begun in FY1998; continued in FY2001 and FY2003)
- Developmental/Pilot Projects in Cancer Complementary and Alternative Medicine (CAM): PAR-02-040 (begun in FY2002)
- Director's Challenge: Toward a Molecular Classification of Tumors: http://dc.nci.nih.gov (begun in FY1999)
- Exploratory Grants for Correlative Laboratory Studies and Clinical Trials: PA-98-042 (ongoing)
- Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses (FLAIR): http://dtp.nci.nih.gov/branches/gcob/gcob_web17.html (begun in FY1998; continued in FY2000 and FY2001)
- Improving DNA, RNA and Protein Availability in Fixed Tissue: PAR-00-079 (begun FY2000)
- *In Vivo* Cellular and Molecular Imaging Centers (ICMICs): http://www3.cancer.gov/bip/ICMICs.htm (begun in FY1999)
- Integrating Aging and Cancer Research: PA-02-169 (begun in FY2002)
- Interdisciplinary Research Teams for Molecular Target Assessment: RFA-CA-00-001 (begun in FY2000)
- Minority-Based Community Clinical Oncology Program (MBCCOP): http://www3.cancer.gov/prevention/ccop/mbccop.html (begun in FY2002)

- Minority Institution/Cancer Center Partnership (MI/CCP): http://minorityopportunities.nci.nih.gov/institutions/ (begun in FY2000)
- Molecular Target Drug Discovery for Cancer: PAR-01-045 and PAR-01-046 (begun in FY2000)
- Mouse Models of Human Cancers Consortium: RFA-CA-98-013 (begun in FY1999)
- NCI Center for Bioinformatics (NCICB): http://ncicb.nci.nih.gov
- Non-Mammalian Organisms as Models for Anticancer Drug Discovery: PAR-99-019 and PAR-99-020 (begun in FY1999)
- Program for the Assessment of Clinical Cancer Tests (PACCT): http://www.cancerdiagnosis.nci.nih.gov/assessment (begun in FY2000)
- Shared Pathology Informatics Networks (SPIN): http://spin.nci.nih.gov/ (begun in FY2000)
- Shared Resources for Scientists Outside NCI Cancer Centers: RFA-CA-01-020 (begun FY1999)
- Small Animal Imaging Resource Program (SAIRP): http://www3.cancer.gov/dip/sairp.htm (begun FY1998)
- Small Grants Program for Cancer Epidemiology: http://epi.grants.cancer.gov/ResPort/grants.html (ongoing)
- Southern Community Cohort Study (SCCS): http://www.southerncommunitystudy.org (begun in FY2001)
- Special Populations Networks (SPNs): http://crchd.nci.nih.gov/spn/index.html (begun FY1999)
- Specimen Resource Locator: http://pluto3.nci.nih.gov/tissue/default.htm (ongoing)
- Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors: RFA-CA-01-011 (expanded in FY2001)
- Therapeutic Modulation of Angiogenesis in Disease: PAR-98-096 (begun FY1998)
- Unconventional Innovations Program (UIP): http://otir.cancer.gov/tech/uip.html (begun in FY1999)

Chapter 3: Biology

- Bioengineering Nanotechnology Initiative: PA-02-125 (begun FY2000; continued in FY2002)
- Complex Formation in Hormonal Regulation of Gene Expression: PA-02-100 (begun in FY2002)
- Mammalian Gene Collection: http://mgc.nci.nih.gov/Info/Summary (begun in FY1999)
- Molecular and Cellular Biology of Metastatic Tumor Cells: PA-01-020 (begun in FY2001)
- Molecular Interactions Between Tumor Cells and Bone: RFA-CA-03-013 (begun in FY2002)
- Structural Biology of Membrane Proteins: PA-02-108 and PA-02-060 (ongoing)

Chapter 4: Etiology

- Cancer Genetics Network (CGN): http://epi.grants.cancer.gov/CGN (ongoing)
- Cohort Studies in Cancer Epidemiology: PAS-02-009 (begun in FY2002)
- Diet, Lifestyle, and Cancer in U.S. Special Populations: PA-98-028 (begun in FY1998)
- Geographic-Based Research in Cancer Control and Epidemiology: PAS-00-120 (begun in FY2000)
- Interdisciplinary Studies in the Genetic Epidemiology of Cancer: RFA-CA-98-018 (begun in FY1998)
- NCI Cohort Consortium: http://cancercontrol.cancer.gov/bb/cohort_conso.html (begun in FY2000)

Chapter 5: Prevention

- Chemoprevention in Genetically-Identified High-Risk Groups: Interactive Research and Development Projects: RFA-CA-98-012 (begun in FY1998)
- Phase I and II Cancer Prevention Clinical Trials Consortia: CN-25000-39 (begun in FY2002)
- Rapid Access to Preventive Intervention Development (RAPID) Program: http://www3.cancer.gov/prevention/rapid/index.html (begun in FY2000)

Chapter 6: Early Detection, Diagnosis, and Prognosis

- Cancer Diagnosis Program: http://www.cancerdiagnosis.nci.nih.gov (ongoing)
- Clinical Proteomics Program (CPP): http://ncifdaproteomics.com/index.php (begun in FY1999)
- Development of Clinical Imaging Drug Enhancers (DCIDE): http://www3.cancer.gov/bip/DCID_des.htm (begun in FY2000)
- Development of Novel Technologies for *InVivo* Imaging: PAR-01-101 and PAR-01-102 (begun in FY2000 as the Development of Novel Imaging Technologies)
- Diagnostic Imaging Network—American College of Radiology Imaging Network (ACRIN): http://www.acrin.org/ (begun in FY1999)
- Early Detection Research Network: http://www3.cancer.gov/prevention/cbrg/edrn (begun in FY1998)
- Exploratory/Developmental Grants for Diagnostic Cancer Imaging: PA-01-030 (begun in FY1998)
- Exploratory Studies in Cancer Detection, Prognosis and Prediction: PA-03-003 (begun in FY2001)
- Exploratory Studies in Cancer Diagnostics: PA-98-022 (begun in FY1998)
- Gene Expression Data Portal (GEDP): http://gedp.nci.nih.gov/dc/index.jsp (ongoing)
- Innovative Technologies for the Molecular Analysis of Cancer: PAR-01-105 and PAR-01-104 (begun in FY1998; continued in FY1999 and FY2001)
- Tissue Array Research Program (TARP): http://ccr.cancer.gov/tech_initiatives/tarp

Chapter 7: Treatment

- Cancer Drug Discovery: Diversity Generation and Smart Assays: RFA-CA-98-009 (ongoing)
- Cancer Therapy-Related Use of Genetically Engineered Mice: PAR-02-051 (begun in FY2002)
- Cancer Trials Support Unit: http://www.ctsu.org (ongoing)
- Central Institutional Review Board: http://www.ncicirb.org/ (begun in FY2001)
- Clinical Cancer Therapy Research: PA-02-002 (continued in FY1999)
- Cooperative Planning Grant for Cancer Disparities Research Partnership: RFA-CA-03-018 (begun in FY2002)
- Development and Application of Imaging in Therapeutic Studies: RFA-CA-98-024 (begun in FY1998)
- Expanded Participation Project (EPP): http://spitfire.emmes.com/study/epp
- National Cooperative Drug Discovery Groups (NCDDGs): http://dtp.nci.nih.gov/branches/gcob/gcob_web3.html (continued in FY1999)
- Quick Trials for Novel Cancer Therapies: PAR-03-005 (begun in FY2000)

- Rapid Access to Intervention Development (RAID) Program: http://dtp.nci.nih.gov/docs/raid/raid_index.html (ongoing)
- Rapid Access to NCI Discovery Resources (RAND): http://dtp.nci.nih.gov/docs/rand/rand_index.html (ongoing)
- Translational Research Initiative (TRI): http://ctep.cancer.gov/resources/trf-overview.html (begun in FY2001)

Chapter 8: Cancer Control, Survivorship, and Outcomes

- Basic Biobehavioral Research on Cancer-Related Behaviors: RFA-CA-99-014 (begun in FY2000)
- Cancer Control PLANET: http://cancercontrolplanet.cancer.gov/ (begun FY2003)
- Cancer Intervention and Surveillance Modeling Network (CISNET): http://cisnet.cancer.gov/about (begun in FY1999; continued in FY2002)
- Cancer Outcomes Measurement Working Group (COMWG): http://outcomes.cancer.gov/methods/measures/comwg (begun in FY2001)
- Cancer Surveillance Using Health Claims-Based Data System: http://dccps.nci.nih.gov/ARP/research/health.asp (continued in FY1999)
- Cancer Survivorship Studies in Established Epidemiologic Cohorts: PA-98-027 (begun in FY1998)
- Centers for Complementary and Alternative Medicine Research: RFA-AT-00-001 (begun in FY1999)
- Centers of Excellence in Cancer Communications Research: http://cancercontrol.cancer.gov/eocc/ (begun in FY2001)
- Digital Divide Pilot Projects: http://cancercontrol.cancer.gov/eocc/ddpp_awards.html (begun in FY2000)
- Economic Studies in Cancer Prevention, Screening, and Care: http://cancercontrol.cancer.gov/ARP/research/economic.asp (ongoing)
- Exploratory Grants for Behavioral Research in Cancer Control: PA-99-163 (begun in FY1999)
- Health Communications in Cancer Control: RFA-CA-98-014 (begun in FY1998)
- Long-Term Cancer Survivors: Research Initiatives: RFA-CA-04-003 (begun in FY1998)
- Minority and Underserved Cancer Survivors: http://cancercontrol.cancer.gov/ocs/underserved
- Research on the Impact of Cancer on the Family: http://dccps.nci.nih.gov/bb/research_family.html
- Research Supplements for Underrepresented Minorities: http://cancercontrol.cancer.gov/ocs/underrepresented/
- SEER-Medicare Linked Database: http://healthservices.cancer.gov/seermedicare (ongoing)
- SEER Patterns of Care/Quality of Care (POC/QOC) Initiative: http://cancercontrol.cancer.gov/bb/seer_pattern.html (begun FY2001)
- Small Grants Program for Behavioral Research in Cancer Control: http://dccps.nci.nih.gov/smallgrants/index.html (ongoing)
- Social and Cultural Dimensions of Health: PA-02-043 (begun in FY2002)
- Surveillance, Epidemiology, and End Results (SEER): http://seer.cancer.gov (expanded in FY2001)
- Translating Research into Improved Outcomes (TRIO): http://cancercontrol.cancer.gov/bb/trio.html

Resources for Breast Cancer Research That Were Developed, Maintained, or Expanded

NCI-funded resources that support breast cancer research include the following:

- Repositories for accessing biological specimens and associated clinical data from patients with breast cancer and women at risk of developing the disease
- Databases for accessing information from multiple sources
- Animal models that mimic the development and/or progression of breast cancer
- Forums for communicating research results and stimulating discussion and collaboration among investigators
- Training programs for improving the skills and advancing the careers of young, mid-career, and minority investigators
- Tools for assisting investigators in locating research resources
- Rapid development of new technologies
- Conduct of large, multi-institutional clinical trials
- Access to specialized patient populations
- Access to specialized equipment and expertise

Examples of NCI-supported resources include the following:

- Cancer Research Training, Career Development, and Education Opportunities
- Cooperative Breast Cancer Tissue Resource
- Mouse Models of Human Cancers Consortium (MMHCC)
- Mammary Gland Cancer Committee
- Mouse Models Repository
- Clinical Trials Cooperative Group Program
- American College of Radiology Imaging Network (ACRIN)
- Early Detection Research Network (EDRN) (which includes a Breast and Gynecologic Cancers Collaborative Group)
- Minority Institution/Cancer Center Partnership (MI/CCP)
- Rapid Access to Intervention Development (RAID) Program

In addition, Specialized Programs of Research Excellence (SPOREs) in Breast Cancer provide a comprehensive mix of translational research projects,[13] core resources, and training opportunities. Details about these SPOREs can be found in Chapter 2.

13 Translational research aims to move findings from the basic laboratory into the clinical setting.

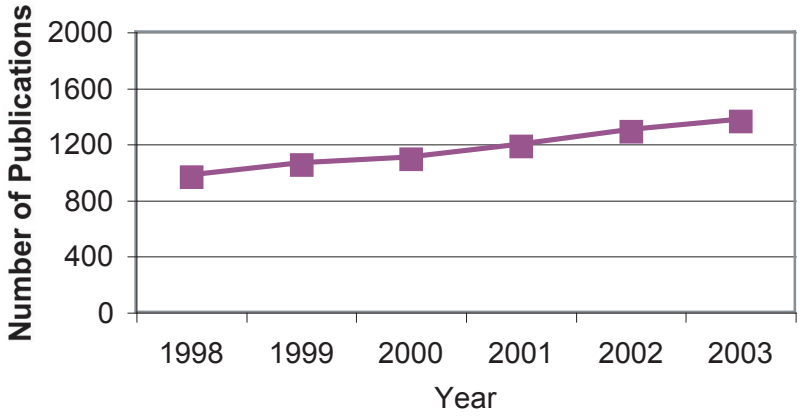

Figure 1-8. Estimated number of peer-reviewed publications on breast cancer acknowledging NCI support
Values are the total unique publications identified from a MEDLINE search and an ISI/Web of Science search. (Both databases were queried using the following criteria: (1) using terms related to "breast"; (2) including an NCI grant number or author address; and (3) limiting to publications in an English-language, peer-reviewed journal. An additional search in MEDLINE for all grant numbers representing 100% breast cancer-relevant projects was performed in the grant number field using the same limitations. Both intramural and extramural NCI projects are represented.)

Research Progress

One indicator of research progress is growth in the number of peer-reviewed publications on a specific topic. Figure 1-8 (page 12) shows the estimated number of peer-reviewed publications indicating NCI support and relevance to breast cancer during calendar years 1998 through 2003. The values in Figure 1-8 should be considered conservative estimates.[14]

Table 1-2 lists areas of ongoing NCI-sponsored research that are represented in recent publications. The table also includes the report chapter in which progress in these areas is highlighted.

Table 1-2. Recent Progress in Breast Cancer Research

Initiatives *(Chapter 2)*

- Specialized Programs of Research Excellence (SPOREs)
  - Krüppel-Like Transcription Factor (KLF4) Protein as a Biomarker
  - Novel Liposome Constructs for Drug Delivery
  - Collaborative Study of Magnetic Resonance Imaging to Measure Response to Chemotherapy
  - AVON Foundation-NCI Progress for Patients Awards Program

Biology *(Chapter 3)*

- Mammary Gland Development and Breast Cancer Susceptibility
  - Breast Cancer Stem Cells
  - Mouse and Multicell Model Systems
- Genetic and Epigenetic Changes in Breast Cancer Development
  - BRCA1 Tumor-Suppressor Gene
  - Her2/*neu*-Receptor Tyrosine Kinase

14 Given such factors as less-than-complete support acknowledgments by authors, inclusion of only the corresponding author's affiliation in MEDLINE, possible typographic errors in reporting grant numbers, possible data entry errors, and journal policies on support acknowledgments, the publication counts reported in Figure 1-8 are no doubt underestimates.

- Metastasis and Progression
  - Factors Responsible for Osteolysis
  - Models of Metastasis

Etiology *(Chapter 4)*

- BRCA1 and BRCA2
  - Risk of Breast Cancer in Mutation Carriers
  - Modifiers of Breast Cancer Risk Among Carriers
- Other Breast Cancer Susceptibility Genes
  - CHEK2
  - ATM Gene
- Environmental Influences
- Behavioral Factors
  - Hormone Replacement Therapy
  - Obesity
- Endogenous Factors

Prevention *(Chapter 5)*

- Models of Precancerous Biology
  - *Neu* Transgenic Mouse
  - Conditional Knockout of the BRCA1 Gene in the Mammary Epithelium of Mice
- Dietary Factors
  - Low-Fat Diet
  - Natural Products (e.g., Green Tea Polyphenol Epigallocatechin-3 Gallate)
- Prevention Trials
  - Selective Estrogen-Receptor Modulators
  - Retinoids

Detection, Diagnosis, and Prognosis *(Chapter 6)*

- Imaging Technologies
  - Positron Emission Tomography
  - Magnetic Resonance Imaging
  - Convolution Neural Networks
  - Automated Estimation Analysis Tool to Estimate Mammographic Breast Density
- Novel Biologic Markers
  - Mammaglobin Gene
  - Epidermal Growth Factor Receptor
  - 2,6-Cyclolycopene-1,5-Diol
  - Combinations of Markers Identified by Microarray
  - Estrogen Receptor and A1B1 (SRC-3) Protein Expression to Predict Response to Tamoxifen Treatment

Treatment *(Chapter 7)*

- Progress in Preclinical Models
  - C3(1)/SV40 Tag Mice
- *In Situ* Disease
  - Postsurgical Tamoxifen
  - Postoperative Anastrazole
- Operable Disease
  - Adjuvant Treatment for Node-Negative Patients
  - Oncotype Dxtm Breast Cancer Assay
  - Preoperative Chemotherapy
  - Breast-Conserving Surgery and Quality of Life
  - Chemotherapy Intervals
  - Aromatase Inhibitors
- Nonoperable Disease
  - Ongoing Clinical Trials With Chemo- and Biologic Therapies

Cancer Control, Survivorship, and Outcomes Research *(Chapter 8)*

- The Importance of Mammography
  - Tailored Communications
  - The Use of Screening Mammography
- Factors Affecting the Accuracy of Mammography
  - Breast Density
  - Breast Positioning During the Mammogram

- Quality of Care
  - Barriers to Appropriate Follow-Up
  - Disparities in the Care of Women With Breast Cancer
- Survivors' Issues
  - Physical Symptoms After Completing Treatment
  - Social Support and Well-Being
  - Health Behaviors
  - Indirect Morbidity and Disability Costs of Breast Cancer

Applied Research

NCI-sponsored research has led to new and innovative prevention and treatment interventions. In 1998, for example, tamoxifen became the first drug to receive U.S. Food and Drug Administration[15] (FDA) approval for the prevention of breast cancer in high-risk women. Two other drugs, anastrozole (Arimidex®) and letrozole (Femara®), received approval as first-line treatments for postmenopausal women with locally advanced or metastatic breast cancer. Anastrozole was also approved for the adjuvant treatment of postmenopausal women with early breast cancer. The FDA also approved taxanes (paclitaxel [Taxol®] and docetaxel [Taxotere®]) and epirubicin (Ellence™) for women with axillary node involvement. Other drugs have been approved for the treatment of metastases associated with breast cancer. In particular, zoledronic acid (Zometa®) and pamidronate (Aredia®) are now used to treat bone metastases and trastuzumab (Herceptin®) is used for patients whose tumors overexpress the Her2/*neu* gene.

Patients with advanced breast cancer now have more treatment options than ever before. For hormone-sensitive tumors, fulvestrant (Faslodex®) and exemestane (Aromasin®) are second-line choice, while a series of new agents—capecitabine (Xeloda®), gemcitabine (Gemzar®), and vinorelbine (Navelbine®)—are new chemotherapeutics able to offer palliation once hormonal therapies become ineffective.

Newer practices related to surgical management of breast cancer have become more accepted.[16] While axillary lymph node dissection remains the standard practice for staging lymph nodes, sentinel lymph node biopsy is receiving greater recognition as an alternative that has the potential to reduce the side effects associated with axillary lymph node dissection. A definitive trial (NSABP B-32) supported by NCI comparing the two approaches has completed accrual of more than 5,000 patients. When available, results from this comparison will prove whether or not the sentinel node technique produces comparable survival results with fewer side effects.

Preoperative (neoadjuvant) therapy can reduce the size of a large tumor, thereby allowing more women to undergo breast-conserving therapy. This approach also holds the appealing possibility of providing for more tailored therapy according to the biologic characteristics and responsiveness of individual tumors. NCI-supported studies are currently enrolling patients on trials testing this novel approach, and these studies are collecting valuable tissue specimens that will be key to an understanding of tumor responsiveness and resistance to specific therapies. More details about preoperative therapy are presented in the Ongoing NCI Research: Operable Disease section of Chapter 7.

U.S. patents issued each year with relevance to breast cancer show promise for future product development. Investigators supported by the NCI have translated their basic discoveries into advances in technology. Between 1998 and 2003, 96 patents

15 Information on breast cancer-related drugs approved by the FDA between 1998 and 2003 was obtained from the FDA's Oncology Tools Web site at http://www.fda.gov/search/databases.html.

16 The American College of Radiologists (ACR) published guidelines on sentinel lymph node biopsy and preoperative therapy in the "Standards for breast conservation therapy in the management of invasive breast carcinoma." This document and other guidelines can be found on the National Guideline Clearinghouse Web site (www.guideline.gov).

relevant to breast cancer were awarded or were pending decisions by the U.S. Patent Trademark Office (USPTO).[17] A listing of these patents can be found in Appendix C, including patents for:

- Advances in breast imaging devices
- Biomarker-based diagnostic and prognostic indicators
- Methods of inhibiting cancer growth
- Assays for tumor proliferative status
- Genetic markers for cancer
- Novel delivery systems for anticancer agents

This Progress Report

This report, which documents the NCI's responsiveness to the recommendations of the Breast Cancer PRG report over the years 1998 through 2003, will be used by the NCI to help the Institute make course corrections and develop new recommendations regarding breast cancer research. The report is organized according to the CSO[18] categories used by the NCI:

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

Chapter 2 provides details on NCI initiatives that address multiple categories of breast cancer research, along with the specific programs, resources, and/or research projects that derive from those initiatives. In Chapters 3 through 8, progress is reported for both a specific research category as a whole and for the underlying individual PRG investigative priorities. Quantitative measures are included throughout to demonstrate the extent of the NCI's responsiveness to the PRG research priorities.

This report addresses only part of the progress made since 1998, with the content limited to NCI-sponsored research that is most relevant to breast cancer. In addition to the NCI, other federal and nonfederal agencies fund research on breast cancer. Furthermore, human cancers are complex diseases; each cancer site has features that are unique and features that are shared with other cancer sites. It is possible that the solution for preventing breast cancer or the suffering and death resulting from this disease will ultimately derive from research directed at another cancer site, or even from research directed at a noncancerous disease. To increase the likelihood that significant breakthroughs will be made in prevention, diagnosis, and treatment, the NCI remains committed to planning, conducting, and assessing research that is directed specifically at breast cancer while remaining ever vigilant for cross-cutting advances from other tumors or disciplines.

17 Patents and patent applications were identified by searching the USPTO databases (http://www.uspto.gov/patft/index.html) for breast-relevant terms and then selecting for projects in which the government interests/rights were attributed to grants that included the NCI's Administering Organization Code.

18 Scientific model systems was not included as a unique chapter in this report due to the small number of priorities addressing this topic in the PRG's original report and the overlapping relevance of this category to other research categories. Significant advances in models research are presented in the chapters on biology, prevention, and treatment.