National Cancer Institute

Breast Cancer Progress Report

Addressing the Recommendations of the Breast Cancer Progress Review Group

October 2004

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
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From the Working Group

It is our pleasure to submit the Breast Cancer Progress Report to the Director of the National Cancer Institute (NCI). It constitutes the first assessment of progress in addressing the research priorities identified in the 1998 report of the Breast Cancer Progress Review Group (PRG) entitled *Charting the Course: Priorities for Breast Cancer Research*. This progress report characterizes trends in the NCI breast cancer research portfolio from 1998 to 2003. It presents trends in measures of progress as broad as overall NCI funding levels and as specific as numbers of projects relevant to particular research priorities.

This report is designed to assist the Institute in efforts to accelerate progress against breast cancer by assessing past research investments and identifying future research needs. It is a unique reference documenting NCI-supported breast cancer research and the resources available to the breast cancer research community. We believe that this report will enable readers to better understand the scope of the Institute's breast cancer research portfolio and identify research and information resources.

Respectfully,

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Acknowledgments

The development of this progress report by the NCI Breast Cancer Working Group would not have been possible without significant contributions from many other individuals. We would especially like to recognize the work of the following individuals and organizations.

- Jim Corrigan, Kevin Callahan, and other staff of the NCI Office of Science Planning and Assessment (OSPA) made contributions in a variety of areas, including expertise on the PRGs, knowledge of NCI initiatives and programs, development of measures of progress, design of the process for mapping NCI-funded projects to PRG priorities, participation in working group meetings, and review of draft documents.
- The following NCI staff provided expertise on the current and recent research activities of the NCI: Barbara Dunn and Ronald Lubet of the Division of Cancer Epidemiology and Genetics and Tracy Lugo-Lively of the Division of Cancer Treatment and Diagnosis. From the Division of Cancer Control and Population Sciences, Helen Meissner, Gary Kreps, Veronica Chollette, Robin Yabroff, Joan Warren, Martin Brown, Joe Lipscomb, and Nancy Breen identified areas of progress in their respective programs and the relevance of their grants to the original PRG priorities.
- Other NCI staff contributed essential data. Brenda Edwards and Lynn Ries of the Surveillance Epidemiology and End Results (SEER) program in the Division of Cancer Control and Population Sciences (DCCPS) provided expertise and data on trends in disease statistics. Lakshmi Grama of the Office of Cancer Information Products and Systems (CIPS) and Teri Brown of the Office of the Deputy Director for Extramural Science contributed expertise and data on clinical trials. Staff of the Financial Management Branch (FMB) provided information on breast cancer research funding. Staff in the Division of Extramural Activities (DEA), the Center for Cancer Research (CCR), and the Division of Cancer Epidemiology and Genetics (DCEG) provided data on extramural and intramural NCI-sponsored research projects.
- The staff of Science Applications International Corporation (SAIC) contributed significant technical expertise and dedicated effort to the management, analysis, technical writing, and production of the report. SAIC's efforts were led by Jeff Zalatoris and Catherine Hall. Significant contributions were made by Deborah Berlyne, Karen Rulli, Sabina Robinson, Anita Sabourin, Quentin Scott, Glenn Bell, Joel Glover, Adam Book, Beth Mathews-Bradshaw, and their colleagues.
- The staff of NOVA Research Company, led by Vicki Butz and Ed Rorie, managed the layout and preparation of the final report.
- The staff of Constella Group, particularly Paul Nedzbala and Jeffrey Morris, assisted in assembling data on the NCI's breast cancer research portfolio.

Executive Summary

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. An estimated 215,000 new breast cancer diagnoses and 40,000 breast cancer deaths are expected in 2004. White women have the highest breast cancer incidence rates, followed by African-American women. While overall mortality due to breast cancer has been declining during the past decade, the rate for African-American women is greater than that for women of other racial/ethnic groups. These recent trends of stabilizing incidence and decreasing mortality rates are encouraging, but breast cancer remains a major health burden for American women and requires continued action.

In 1997, the National Cancer Institute (NCI) convened the Breast Cancer Progress Review Group (PRG), a multidisciplinary working group of scientists, clinicians, and advocates, to help NCI define a national research agenda for breast cancer. The Breast Cancer PRG issued a 1998 report entitled *Charting the Course: Priorities for Breast Cancer Research*, which included research questions that should be addressed to advance prevention, detection, diagnosis, and treatment of breast cancer. An internal NCI Breast Cancer Working Group was convened in 2004 to assess the research progress made since the release of this report.

The NCI Breast Cancer Progress Report documents trends in the NCI breast cancer research portfolio from 1998 to 2003. Multiple measures of progress are presented at varying levels of specificity, ranging from overall trends in NCI funding, projects, and resulting peer-reviewed publications to more specific trends in the number of projects relevant to particular research priorities identified by the PRG.

Between 1998 and 2003, NCI substantially expanded investments in breast cancer research, as evidenced by:

- Increasing breast cancer funding by nearly 60%, from $348.6 million in 1998 to $548.7 million in 2003.
- Increasing the number of relevant projects by 60%.
- Expanding ongoing and initiating new programs to sustain and advance both basic and clinical breast cancer research.
- Expanding the Breast Specialized Programs of Research Excellence (SPOREs) network from 4 to 10 sites.
- Expanding collaborative efforts, public-private partnerships, and shared resources to improve the capacity to conduct breast cancer clinical trials.

During these years, new and innovative types of treatment, preventive measures, and diagnostic techniques have been developed and approved or are being studied in clinical trials, including:

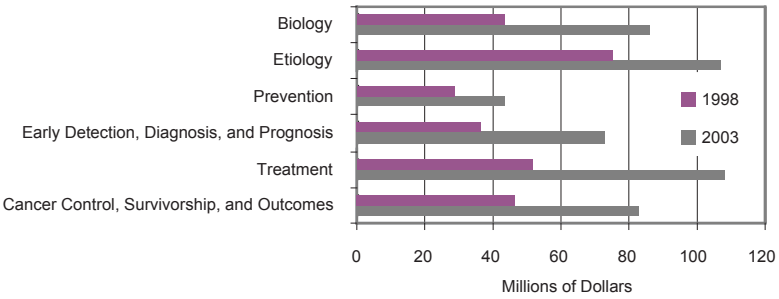
- Tamoxifen (Nolvadex®) for the prevention of breast cancer in high-risk women.
- Aromatase inhibitors (anastrozole, exemestane) for treatment of estrogen receptor-positive breast cancer.
- Monoclonal antibodies (Herceptin®) for treatment of tumors that express Her2/ErbB2.
- Sentinel node biopsy for less-invasive surgical diagnosis and prognosis.
- Lumpectomy with radiation as an equivalent alternative to mastectomy for certain stages of disease.
- Preoperative (neoadjuvant) therapy to reduce the size of large tumors, thereby allowing more women to undergo breast-conserving therapy.

Work is under way to translate the discoveries generated by this expanded investment into new breast cancer prevention, detection, diagnosis, and treatment interventions that will save lives. The following two pages summarize NCI's investment by research category.

NCI's ability to capitalize on advances in breast cancer research and care will require continued basic, translational, and clinical research support. This progress report, which documents NCI's responsiveness to the recommendations of the Breast Cancer PRG, will help guide the Institute's efforts to make course corrections and develop new recommendations regarding breast cancer research.

NCI's Breast Cancer Research Investment

NCI's breast cancer research investment increased from $348.6 million in 1998 to $548.7 million in 2003.



Growth of NCI's Investment in Extramural Research by Scientific Category

Biology

- Funding increased from $43.2 million to $86 million.
- The number of projects increased from 257 to 504.
- New initiatives included the Bioengineering Nanotechnology Initiative, Complex Formation in Hormonal Regulation of Gene Expression, the Mammalian Gene Collection, and Molecular and Cellular Biology of Metastatic Tumor Cells.

Etiology

- Funding increased from $75.3 million to $107.2 million.
- The number of projects increased from 263 to 424.
- New initiatives included Breast Cancer and the Environment Research Centers, Cohort Studies in Cancer Epidemiology, Interdisciplinary Studies in the Genetic Epidemiology of Cancer, and the NCI Cohort Consortium.

Prevention

- Funding increased from $28.9 million to $43.7 million.
- The number of projects increased from 190 to 295.
- New initiatives included Chemoprevention of Estrogen Receptor-Negative Breast Cancer Preclinical Studies, Phase I and II Cancer Prevention Clinical Trials Consortia, the Study of Tamoxifen and Raloxifene (STAR) Trial, and the Rapid Access to Preventive Intervention Development Program.

Early Detection, Diagnosis, and Prognosis

- Funding increased from $36.4 million to $73.2 million.
- The number of projects increased from 197 to 288.
- New initiatives included Development of Digital Mammography Displays and Workstations, Development of Novel Technologies for *In Vivo* Imaging, the Diagnostic Imaging Network–American College of Radiology Imaging Network, the Early Detection Research Network, and Innovative Technologies for the Molecular Analysis of Cancer.

Treatment

- Funding increased from $52 million to $108.2 million.
- The number of projects increased from 302 to 493.
- New initiatives included Cancer Therapy-Related Use of Genetically Engineered Mice, Development and Application of Imaging in Therapeutic Studies, Quick Trials for Novel Cancer Therapies, and the Translational Research Initiative.

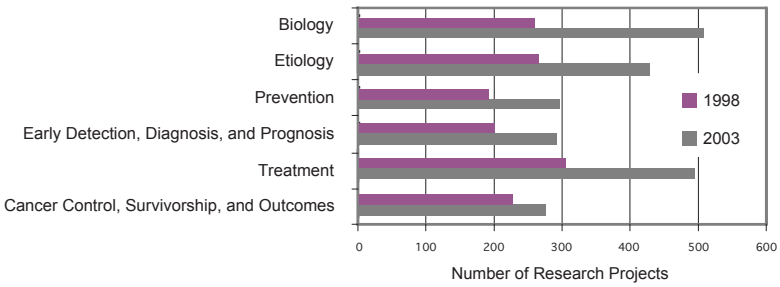
Cancer Control, Survivorship, and Outcomes

- Funding increased from $46.6 million to $82.8 million.
- The number of projects increased from 224 to 274.
- New initiatives included Cancer Control PLANET, Centers of Excellence in Cancer Communications Research, Exploratory Grants for Behavioral Research in Cancer Control, Health Communications in Cancer Control, and Minority and Underserved Cancer Survivors.

Examples of Progress Resulting from NCI's Breast Cancer Research Investment

Biology

- Recent advances include new mouse models that mimic breast cancer in humans, the discovery of factors that contribute to mammary tumorigenesis, and elucidation of the functional characteristics of mammary epithelial stem cells.
- Future investment is needed in the areas of normal mammary development and the integration of biological information across various model systems.



Growth of NCI's Breast Cancer Research Program by Scientific Category

Etiology

- Recent advances include the identification of new breast cancer susceptibility genes, determining environmental influences on breast cancer development, and identifying behavioral risk factors.
- Future investment is needed in validating the association and causation of putative susceptibility genes with breast cancer risk, identifying linkages between genes and the environment, and understanding the role of endogenous hormones.

Prevention

- Recent advances include the development of new models of precancerous biology, determining the association between the consumption of certain dietary components and reduced breast cancer risk, and identifying effective strategies for reducing breast cancer incidence.
- Future investment is needed in developing an intervention strategy that reduces the incidence of both ER-positive and ER-negative breast cancer and determining why some of the women who use preventive interventions like tamoxifen develop breast cancer in spite of the intervention.

Early Detection, Diagnosis, and Prognosis

- Recent advances include the development of novel digital imaging devices, newly identified biologic markers, and the use of computers to improve the diagnostic accuracy of breast imaging.
- Future investment is needed in improving the sensitivity and specificity of screening film mammography and the reproducibility of computer-aided devices and determining the uses of newly identified biomarkers.

Treatment

- Recent advances include improved treatment of *in situ* disease, refinements in all aspects of the traditional treatment paradigm, and treatments that prolong survival in women with nonoperable breast cancer while maintaining quality of life.
- Future investment is needed in the development of noninvasive approaches for primary breast cancer ablation and integrating noninvasive imaging techniques to better appreciate the activity and mechanism of action of targeted therapies in Phase I and II studies.

Cancer Control, Survivorship, and Outcomes

- Recent advances include techniques to increase the number of women screened for breast cancer, examining the impact of breast density and breast positioning on mammographic accuracy, and understanding the impact of social support on survivors' well-being.
- Future investment is needed in communications strategies to educate more women about the importance of mammography, increasing the rate at which underserved populations are screened for breast cancer, and ways to increase the accuracy with which mammograms are interpreted.

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.

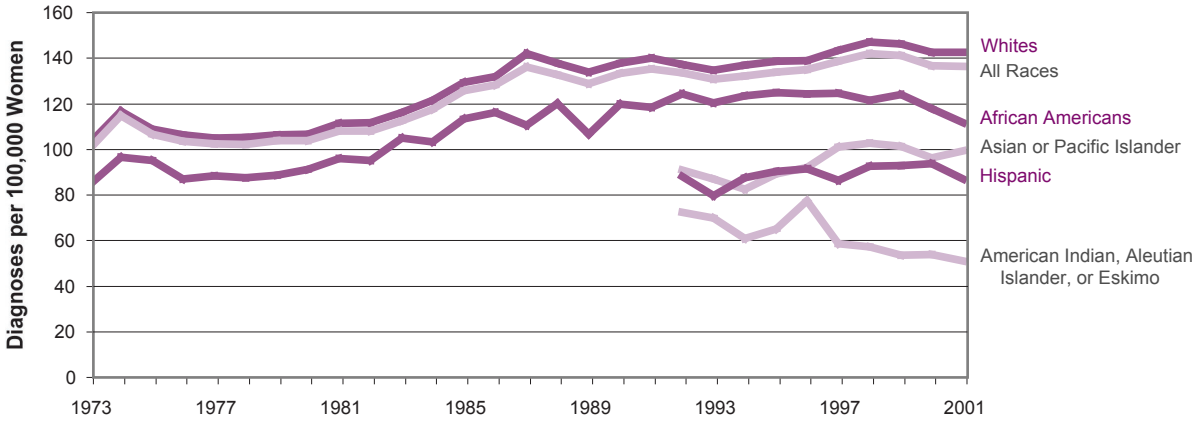


Figure 1-1. Breast cancer incidence in the United States
Data derived from NCI's SEER Program

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.

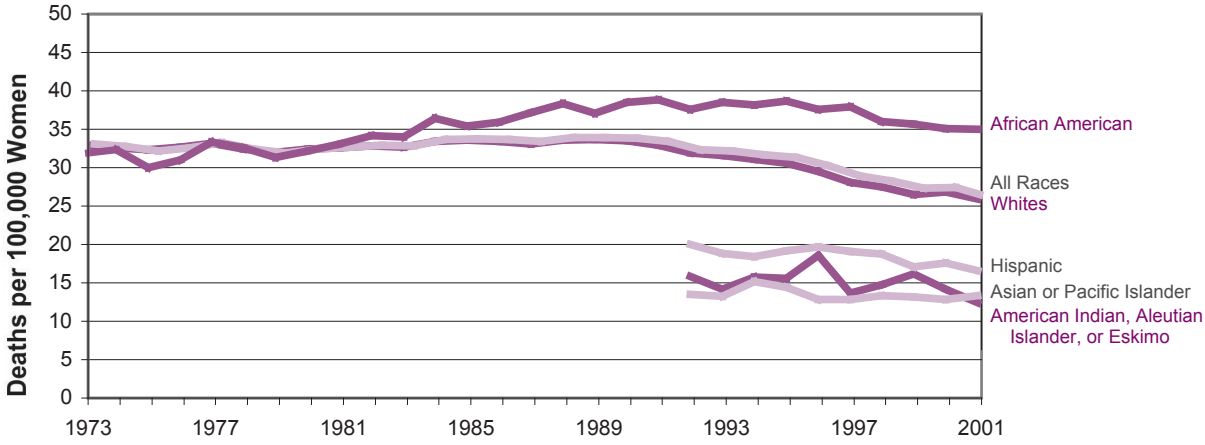


Figure 1-2. Breast cancer mortality in the United States

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]

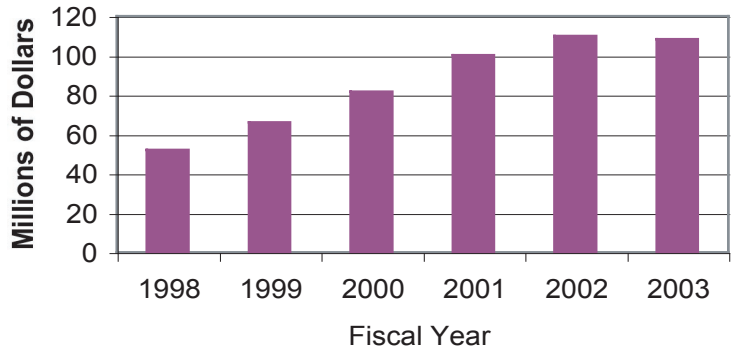


Figure 1-3. Estimate of total NCI dollars for breast cancer-relevant research

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.

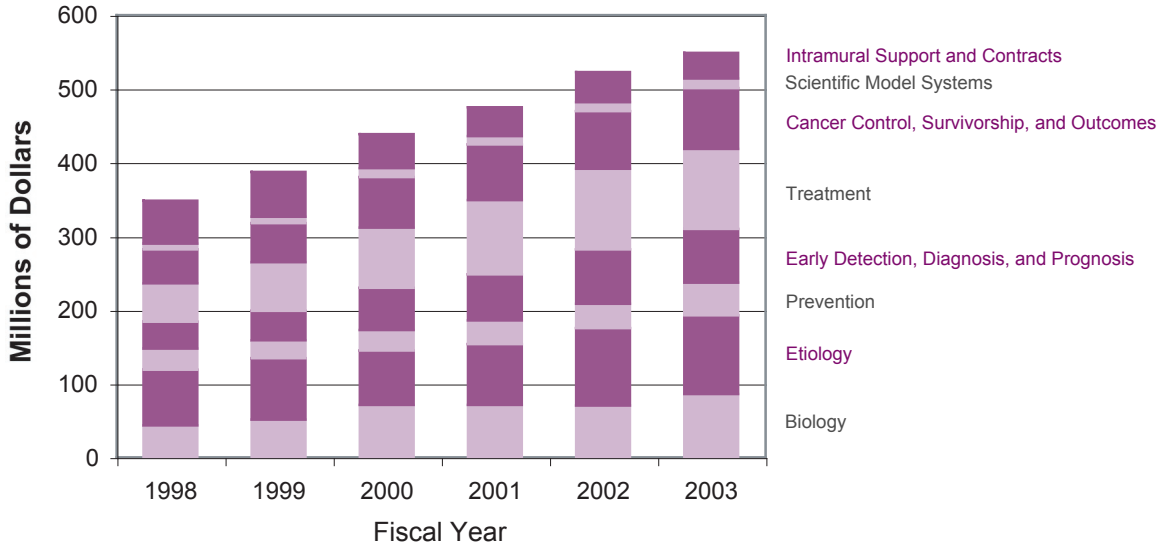


Figure 1-4. Dollar estimates for breast cancer-relevant research by type of research

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].

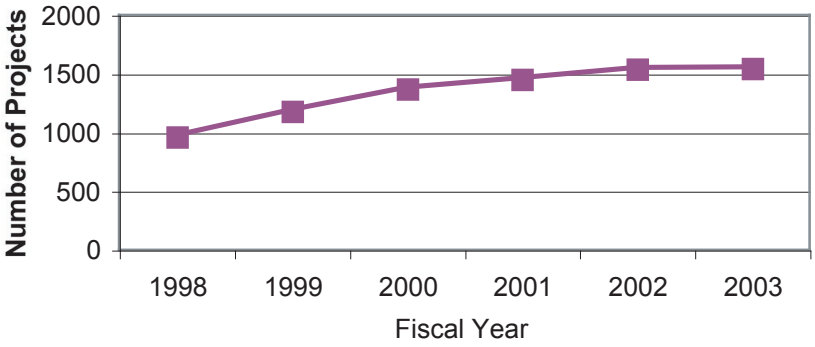


Figure 1-5. Number of research projects relevant to breast cancer

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.

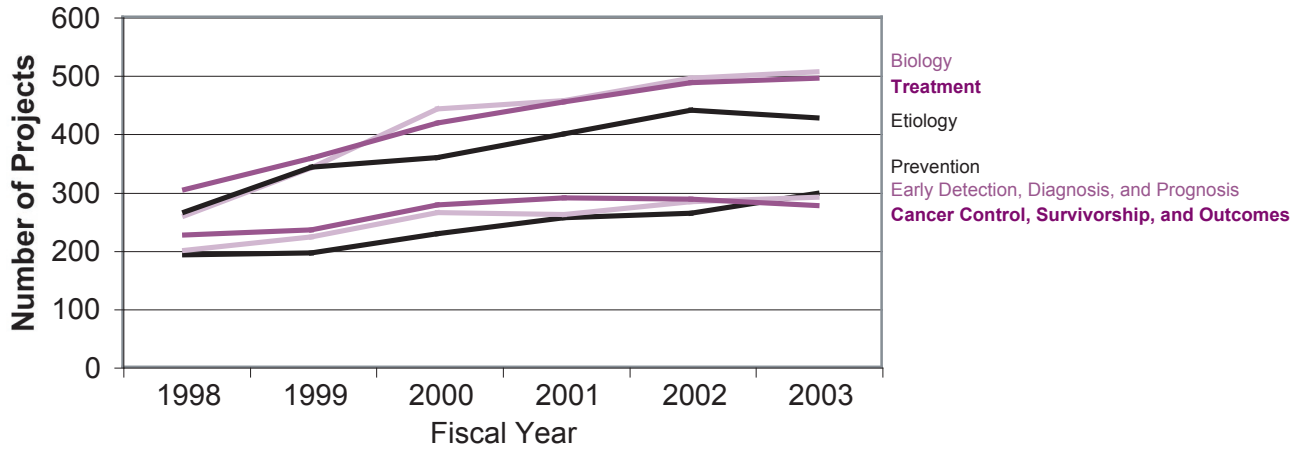


Figure 1-6. Number of breast cancer-relevant projects addressing each research category

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.

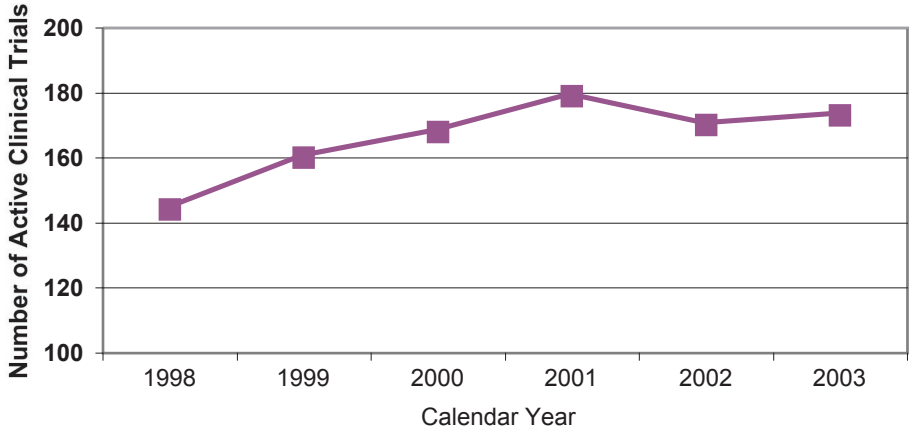


Figure 1-7. Number of NCI-sponsored breast cancer clinical trials active during calendar years 1998-2003

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.

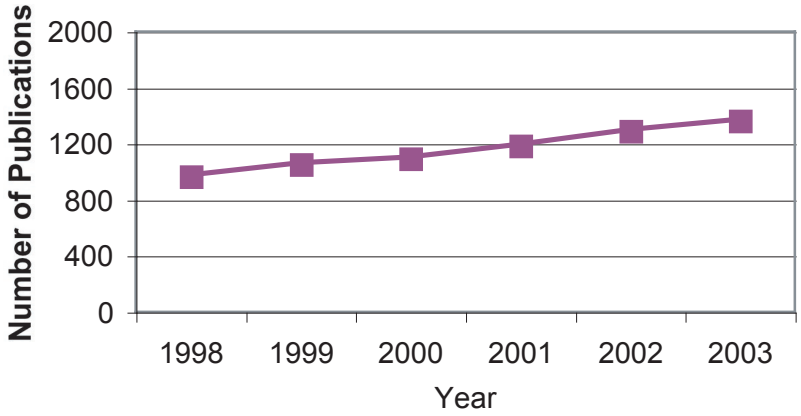


Figure 1-8. Estimated number of peer-reviewed publications on breast cancer acknowledging NCI support
Values are the total unique publications identified from a MEDLINE search and an ISI/Web of Science search. (Both databases were queried using the following criteria: (1) using terms related to "breast"; (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.

Chapter 2: Initiatives

The current mechanism of peer-reviewed, investigator-initiated research project grants has served us very well over the years. This approach should be continued and enhanced.… Additional pathways are needed, however, to support important research not currently well served by existing mechanisms. *Charting the Course: Priorities for Breast Cancer Research*

As the leader of the National Cancer Program, the NCI provides vision and direction to the nationwide community of researchers, public health workers, health care providers, patients, advocates, and policy makers working to defeat cancer. In this capacity, the NCI is responsible for coordinating, conducting, and funding programs in basic research, training, and public health that pertain to the diagnosis, prevention, and treatment of cancer.

The largest share of NCI funding for biomedical research supports investigator-initiated applications. This approach enables individual scientists to design and focus on research projects that they believe have the greatest significance and offer the best chance of producing important knowledge. The investigator-initiated cancer research portfolio extends broadly across research fields and disciplines.

Research is also solicited and resources are developed through the use of *initiatives*, which encourage work in priority areas, support multidisciplinary research collaborations, and generate research applications in areas that are not addressed adequately. Initiatives permit the NCI to take advantage of scientific opportunities in a timely way. They also provide funding to overcome barriers to progress and allow investigators to pursue new research that is outside their area of expertise. Initiatives soliciting breast cancer research are used by the NCI to address priorities that might not otherwise be addressed through investigator-initiated research proposals. In the broadest sense, initiatives include the following:

- The extramural funding opportunities used for establishing new projects, resources, and programs
- The resources and programs that result from these funding opportunities
- The resources and programs that the NCI establishes within its intramural programs

A recurring theme throughout the 1998 Breast Cancer PRG report was that progress in highly promising avenues of breast cancer research is being delayed because of limitations in knowledge, resources, infrastructure, or capacity needed for conducting this work. To address these limitations, PRG members generated a list of the most important scientific priorities and recommended actions in breast cancer biology, etiology, genetics, prevention, detection, treatment, cancer control, and outcomes. These topics are addressed in Chapters 3-8 of this report. In addition to these recommendations, the 1998 Breast Cancer PRG identified 13 critical areas of equal priority spanning the continuum of breast cancer research and care:

- Increase basic research on the biology and developmental genetics of the normal mammary gland.
- Develop better model systems for breast cancer.
- Increase research on the genetics and biology of precancerous lesions and their progression to invasive, metastatic cancers.
- Identify key biomarkers and surrogate endpoints for epidemiologic studies and prevention and therapy trials.
- Enhance availability of new technologies and funding for equipment.
- Facilitate novel therapeutic approaches in academic health centers and via public/private partnerships.
- Modify and enhance support for prevention and therapy clinical trials.
- Ensure that all breast cancer basic and clinical research and communications efforts reflect and address patient and survivor needs and concerns.

- Increase focus on and support for basic and applied research into biobehavioral mechanisms and decision making relevant to cancer prevention, detection, and treatment.
- Expand training opportunities and support, especially for multidisciplinary training of translational investigators and to attract new talent to breast cancer research.
- Promote multidisciplinary research focus and communication.
- Develop mechanisms to support innovation and enhance support for specific areas of research.
- Address informed consent and confidentiality issues.

The NCI has responded to the 1998 PRG priorities and recommendations by expanding its investment in solicited breast cancer research. By expanding ongoing initiatives and introducing new initiatives targeting priority research topics, the NCI provides focused support and guidance for researchers pursuing breast cancer studies. By supporting initiatives that provide infrastructure and resources, the NCI facilitates research projects that rely on centralized, shared resources and collaborations. Many of these initiatives and resources are, appropriately, not limited to or specific for breast cancer, but their availability facilitates the efforts of those focusing on breast cancer research.

NCI's Investment and Response

Chapter 1 shows the growth in NCI spending on breast cancer research (Figure 1-3) and lists the specific initiatives that addressed breast cancer (Table 1-1) during the period 1998-2003. In this chapter, detailed information is provided for initiatives that are relevant to more than one research category. This information includes a description of the initiative, relevant research categories, and the program, resource, research projects, and/or products that resulted from the initiative (Table 2-1). For each initiative in Table 1-1 that applies to a single research category, more detail is provided in the report chapter that corresponds to the category.

Table 2-1. NCI Initiatives Relevant to Breast Cancer Research: Initiatives Affecting Multiple Research Categories[a]

Initiatives Focused on Breast Cancer

- Aging Women and Breast Cancer (PA-00-001)
  - Overview: Supports research that focuses on the unique problems of older women with breast cancer.
  - Research Categories: All.
  - Relevant Projects Resulting From This PA: Between 1998 and 2003, 11 projects relevant to breast cancer research were supported. Specific projects can be found in Appendix B, Tables B2, B9, B16, B23, B33, B40, B41, B43, B46, B51, B54, and B55, by searching for the current PA number and the previously issued PA number (PA-96-034).
- Breast and Ovarian Cancer Family Registries (CFRs) (http://epi.grants.cancer.gov/BCFR/index.html)
  - Overview: Maintains tissue specimens and treatment information provided by over 9,000 families with a history of breast or ovarian cancer.
  - Research Categories: Etiology; Prevention; Early Detection, Diagnosis, and Prognosis; Treatment; Cancer Control, Survivorship, and Outcomes.
  - Relevant Resource Related to This Initiative: The CFR resources are available to researchers to support studies in genetic epidemiology, clinical investigations, social and behavioral epidemiology, and health policy research. CFR data were used in more than 100 published reports between 1998 and 2003.

a. Lists of projects derived from initiatives can be found on the online Supplement to the Breast Cancer Progress Report: Initiatives Database.

- Breast Cancer Faculty (http://ccr.cancer.gov/faculties/faculty.asp?facid=129)
  - Overview: Facilitates interactions among basic, epidemiological, translational, and clinical researchers in the NCI intramural research program in an effort to promote a community of investigators working together for the prevention, diagnosis, and cure of breast cancer. More than 200 NCI and NIH faculty members participate in a monthly seminar series and annual retreat to facilitate communication and collaborations among laboratories.
  - Research Categories: Biology; Etiology; Prevention; Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Program Resulting From This Initiative: Recent accomplishments include the establishment of consensus nomenclature for the comparative pathology of genetically engineered mouse and human breast lesions and the development of the NCI Mouse Model for Mammary Cancer Collective, which is a component of the Mouse Models of Human Cancers Consortium.
- Breast Cancer Surveillance Consortium (BCSC) (http://breastscreening.cancer.gov/)
  - Overview: Supports studies that investigate the factors influencing screening mammography performance in community practice. In addition to conducting research that evaluates screening mammography and its effect in populations, BCSC is actively collaborating with federal regulatory agencies, radiological professional societies, and private-sector vendors to reduce the cost and improve the quality of screening mammography performance. BCSC reviews and comments on reports and initiatives by these agencies, as well as collaborates in standardizing data collection for mammography quality control. BCSC relies on a Statistical Coordinating Center (RFA-CA-98-025) to serve as the central repository for pooled data and to provide the research expertise on complex statistical issues for analysis of these pooled data.
  - Research Categories: Prevention; Early Detection, Diagnosis, and Prognosis; Cancer Control, Survivorship, and Outcomes.
  - Relevant Projects Resulting From This Initiative:

    Breast Cancer Surveillance in a Defined Population

    Carolina Mammography Registry

    Colorado Mammography Project

    New Hampshire Mammography Network

    New Mexico Mammography Project

    San Francisco Mammography Registry

    Statistical Coordinating Center

    Vermont Breast Cancer Surveillance System
- Cooperative Breast Cancer Tissue Resource (CBCTR) (http://www-cbctr.ims.nci.nih.gov/)
  - Overview: Facilitates large research studies requiring archival tissue by supplying investigators with primary breast cancer tissues and associated clinical data.
  - Research Categories: Biology; Etiology; Prevention; Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Resources Resulting From This Initiative: Investigators can search an online database to identify breast cancer specimens that meet their specific research needs. Searches can be made based on annotated clinical characteristics, which include but are not limited to stage of disease, recurrence information, and treatment received, as well as resource characteristics, including the availability of normal (control) tissue.

- Insight Awards to Stamp Out Breast Cancer (PAR-99-128)
  - Overview: Supports innovative pilot studies to generate a new understanding of breast cancer. The focus of the program is to advance underdeveloped areas of research that were identified by the NCI Breast Cancer Progress Review Group.
  - Research Categories: All.
  - Relevant Products Resulting From This PA: Between 1998 and 2003, 47 projects relevant to breast cancer research were supported through this PA.[b]
- International Breast Cancer Screening Network (IBSN) (http://appliedresearch.cancer.gov/ibsn/)
  - Overview: Supports collaborative research aimed at identifying and fostering effective approaches to worldwide breast cancer control through population-based screening mammography.
  - Research Categories: Early Detection, Diagnosis, and Prognosis; Cancer Control, Survivorship, and Outcomes.
  - Relevant Program Resulting From This Initiative: Representatives from 25 countries work together to compare data from international breast cancer screening programs and to develop methods for evaluating the impact of population-based breast cancer screening programs. Working groups within this consortium include the following:

    Case Control Evaluation Group

    Communications Working Group

    Group on Assessment of Organized Screening Programs

    Mortality Evaluation Group

    Performance Parameters Evaluation Group

    Quality Assurance Group
- Specialized Programs of Research Excellence (SPOREs) in Breast Cancer (http://spores.nci.nih.gov/breast/breast.html)
  - Overview: Supports translational research centers that focus on the prevention, etiology, screening, diagnosis, and treatment of a specific organ-site cancer.
  - Research Categories: All.
  - Relevant Program Resulting From This Initiative: There are currently ten breast cancer SPORE sites, which are listed in Table 2-2. Yearly meetings are held to facilitate communication among the researchers participating in the breast cancer SPOREs and among the researchers participating in SPOREs for all cancer types.

Initiatives With Breast Cancer-Relevant Components

- Applications of Innovative Technologies for the Molecular Analysis of Cancer (PAR-01-106; PAR-01-107)
  - Overview: Supports research projects that evaluate and implement molecular analysis technologies in studies relevant to cancer research.
  - Research Categories: Biology; Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Research Projects Resulting From These PAs: Between 1998 and 2003, 16 projects relevant to breast cancer research were supported. Specific projects can be found in Appendix B, Tables B1, B2, B5, B10, B14, B19, B26, and B29-33, by searching for these current PA numbers and the previously issued PA numbers (PAR-99-102 and PAR-99-103).

b. Lists of projects derived from initiatives can be found in the online Supplement to the Breast Cancer Progress Report: Initiatives Database.

- Basic and Preclinical Research on Complementary and Alternative Medicine (CAM) (PA-02-124)
  - Overview: Provides support for CAM and conventional researchers to focus on basic, mechanistic, and preclinical research on Complementary and Alternative Medicine-based treatments for diseases such as breast cancer.
  - Research Categories: Prevention; Treatment; Cancer Control, Survivorship, and Outcomes.
  - Relevant Projects Resulting From This PA: Pending–this PA will remain open until July 15, 2005.
- Bioengineering Research Grants (PA-02-011)
  - Overview: Supports multidisciplinary research performed in a single laboratory or by a small number of investigators that applies an integrative systems approach to develop knowledge and/or methods to prevent, detect, diagnose, or treat disease or to understand health and behavior.
  - Research Categories: Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Projects Resulting From This PA: Between 1998 and 2003, six projects relevant to breast cancer research were supported. Specific projects can be found in Appendix B, Tables B17, B18, B34, B51, B53, B54, and B56, by searching for the current PA number and the previously issued PA number (PAR-99-009).
- Bioengineering Research Partnerships (PAR-02-010)
  - Overview: Supports the formation of multidisciplinary research partnerships among multiple institutions that apply an integrative systems approach to develop knowledge and/or methods to prevent, detect, diagnose, or treat disease or to understand health and behavior.
  - Research Categories: Biology; Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Projects Resulting From This PA: Between 1998 and 2003, eight projects relevant to breast cancer research were supported. Specific projects can be found in Appendix B, Tables B2, B26, B29, B30, and B39, by searching for the current PA number and the previously issued PA numbers (PA-01-024, PAS-00-006, and PAS-99-010).
- Cancer Biomedical Informatics Grid (caBIG) (http://cabig.nci.nih.gov/)
  - Overview: Provides greater access to data, sharing of informatics tools and resources, and enables collaborations that span across laboratories and institutions. This grid is planned to be capable of expanding beyond the current proposed uses of clinical trials management, basic and clinical research support and data sharing, and tissue bank and pathology support.
  - Research Categories: All.
  - Relevant Resources Resulting From This Initiative: caBIG supports a variety of research applications, including the cancer Image Database (caIMAGE), cancer Model Organisms Database (caMOD), Cancer Central Clinical Database (C3D), and cancer Laboratory Information Management System (caLIMS). Original NCI databases such as the cancer Data Standards Repository (caDSR), Common Data Elements (CDE), CGAP, and CMAP are available to researchers through caBIG, as are tools and applications developed by partner institutions.
- Cancer Centers Program (www3.cancer.gov/cancercenters/)
  - Overview: Supports major academic and research institutions throughout the United States to sustain broad-based, coordinated, interdisciplinary programs in cancer research.
  - Research Categories: All.
  - Relevant Programs Resulting From This Initiative: More than 60 institutions have been awarded P30 Cancer Center Support Grants (CCSG) to fund the scientific infrastructure of their cancer centers. Support is provided for

elements such as scientific leadership and administration, research resources that give ready access to state-of-the art technologies, and flexible funds that help the center pursue its planned objectives and take immediate advantage of new research opportunities.

- Cancer Genetics Services Directory (http://www.cancer.gov/search/genetics_services/)
  - Overview: Supports a directory of individuals who provide services related to cancer genetics, including cancer risk assessment, genetic counseling, and genetic susceptibility testing.
  - Research Categories: Etiology; Cancer Control, Survivorship, and Outcomes.
  - Relevant Resource Resulting From This Initiative: Individuals contemplating genetic testing can locate a genetics counselor by searching an online directory. More than 370 genetics professionals specializing in breast cancer are listed in the United States and Canada.
- Cancer Genome Anatomy Project (CGAP) (http://cgap.nci.nih.gov/)
  - Overview: Supports a collaborative program for determining the gene expression profiles of normal, precancerous, and cancerous cells.
  - Research Categories: Biology; Etiology; Prevention; Early Detection, Diagnosis, and Prognosis.
  - Relevant Resource Resulting From This Initiative: Through the CGAP Web site, researchers can access human and mouse genomic data, informatics tools, and information on methods and resources. The database has more than 20,000 expressed genes from normal or cancerous human mammary tissue. The SAGE Genie Anatomic Viewer tool allows scientists to identify genes uniquely expressed in specific cancers, including breast cancer.
- Cancer Imaging Program (CIP) (http://www3.cancer.gov/dip)
  - Overview: Encompasses multiple initiatives that support cancer-related basic, translational, and clinical research in imaging sciences and technology.
  - Research Categories: Biology; Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Programs Resulting From This Initiative: Breast cancer research has been supported through Requests for Applications (RFAs) for the following programs:

    Development and Application of Imaging in Therapeutic Studies

    Development and Testing of Digital Mammography Displays and Workstations

    Exploratory/Developmental Grants for Diagnostic Cancer Imaging

    In Vivo Cellular and Molecular Imaging Centers (ICMICs)

    Planning Grants for *In Vivo* Cellular and Molecular Imaging Centers (Pre-ICMICs)

    Small Animal Imaging Resource Programs (SAIRPs)
- Cancer Molecular Analysis Project (CMAP) (http://cmap.nci.nih.gov)
  - Overview: Provides access to information regarding various aspects of cancer molecular biology, including molecular signatures for specific cancer types, molecular targeted agents, and clinical trials evaluating these agents.
  - Research Categories: Biology; Prevention; Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Resource Resulting From This Initiative: Data can be retrieved from the CMAP Web site for many types of cancer, including breast cancer.

- Cancer Prognosis and Prediction (PAR-01-061; PAR-01-062)
  - Overview: Supports the development of new strategies for determining prognosis or predicting response to cancer therapy.
  - Research Categories: Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Research Projects Resulting From These PAs: Between 1998 and 2003, five projects relevant to breast cancer research were supported. Specific projects can be found in Appendix B, Tables B29 and B33, by searching for these PA numbers.
- Cancer Research Network (CRN) (http://cancercontrol.cancer.gov/bb/can_research.html)
  - Overview: Supports research on cancer prevention, early detection, long-term care, and postdiagnosis monitoring.
  - Research Categories: Early Detection, Diagnosis, and Prognosis; Cancer Control, Survivorship, and Outcomes.
  - Relevant Resource Resulting From This Initiative: Comprising 11 managed care research organizations, the CRN is developing integrated data systems to support studies that include evaluation of breast and cervical cancer screening and prophylactic mastectomy for women at high risk for breast cancer.
- Cancer Research Small Grant Program (PAR-02-176) and Cancer Prevention Research Small Grant Program (PAR-00-025)
  - Overview: Supports research in the fields of early detection, chemoprevention, biomarker development, and nutrition science. Short-term awards provide support for pilot projects, development and testing of new methodologies, or innovative projects that provide a basis for more extended research.
  - Research Categories: Biology; Etiology; Prevention; Early Detection, Diagnosis, and Prognosis.
  - Relevant Research Projects Resulting From These PAs: Between 1998 and 2003, 30 projects relevant to breast cancer research were supported. Specific projects can be found in Appendix B, Tables B1-3, B6-17, B19, B21, B23, B30, B31, and B36, by searching for these PA numbers.
- Cancer Research Training, Career Development, and Education Opportunities (http://cancertraining.nci.nih.gov/)
  - Overview: Supports predoctoral and postdoctoral training and faculty career development in the field of cancer research.
  - Research Categories: All
  - Relevant Resource Resulting From This Initiative: More than ten types of awards exist to support training and career development in cancer biology, causation, prevention and control, detection and diagnosis, treatment, and rehabilitation research. The number of breast cancer-relevant individual training and career development awards nearly doubled between the years FY1998 and FY2003.
- Clinical Trials Cooperative Group Program (http://ctep.cancer.gov/resources/coop2.html)
  - Overview: Supports organizations that generate and conduct clinical trials consistent with national priorities for cancer research.
  - Research Categories: Etiology; Prevention; Early Detection, Diagnosis, and Prognosis; Treatment; Cancer Control, Survivorship, and Outcomes.
  - Relevant Resource Resulting From This Initiative: The cooperative groups include 14 member organizations, with 11 currently conducting trials on breast cancer. Banked tissue resources are available to investigators through each cooperative group.

- Community Clinical Oncology Program (CCOP) (http://www3.cancer.gov/prevention/ccop)
  - Overview: Supports a comprehensive clinical trials mechanism for disseminating the latest cancer prevention and treatment research findings at the community level.
  - Research Categories: Prevention; Treatment; Cancer Control, Survivorship, and Outcomes.
  - Relevant Program Resulting From This Initiative: The CCOP includes 17 funded groups of hospitals or private practices that participate in NCI-funded clinical trials. Ten of these groups are currently participating in trials on breast cancer.
- Competing Supplements for Organotypic Models of Cancer (PAR-02-052)
  - Overview: Supports the development and use of novel organ-like model systems that more closely resemble normal tissue or emerging tumors than do simple tissue culture systems.
  - Research Categories: Biology; Etiology; Prevention.
  - Relevant Projects Resulting From This PA: Pending.
- Cooperative Human Tissue Network (CHTN) (http://www-chtn.ims.nci.nih.gov/)
  - Overview: Supports the collection and distribution of benign, precancerous, and cancerous human tissue specimens for basic and developmental studies in cancer research.
  - Research Categories: Biology; Etiology; Prevention; Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Resource Resulting From This Initiative: Six member institutions currently coordinate the collection and distribution of specimens that include tissues obtained at surgery and autopsy, serum, and DNA/RNA. A Breast Tissue Progression Microarray is available in collaboration with CBCTR.
- Correlative Studies Using Specimens from Multi-Institutional Treatment Trials (PA-03-064)
  - Overview: Supports correlative studies using tumor specimens collected during multi-institutional trials. Potential studies may address the genetic variations and molecular changes within a cell, discovery of new cancer interventions, and promotion of translational research.
  - Research Categories: Etiology; Prevention; Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Projects Resulting From This PA: Between 1998 and 2003, seven projects relevant to breast cancer research were supported. Specific projects can be found in Appendix B, Tables B2, B29, B30, B34, and B36, by searching for the current PA number and the previously issued PA numbers (PA-98-099 and PA-01-015).
- Developmental/Pilot Projects in Cancer Complementary and Alternative Medicine (CAM) (PAR-02-040)
  - Overview: Encourages and supports the development of basic and clinical (prevention, therapeutic, and palliative) CAM cancer research. Another goal of this initiative is to facilitate communication and collaboration between the CAM practitioner and the conventional cancer research communities.
  - Research Categories: Treatment; Cancer Control, Survivorship, and Outcomes.
  - Relevant Projects Resulting From This PA: Between 1998 and 2003, six projects relevant to breast cancer research were supported. Specific projects can be found in Appendix B, Tables B33, B39, B41, B51, and B53, by searching for the PA number.
- Director's Challenge: Toward a Molecular Classification of Tumors (http://dc.nci.nih.gov)
  - Overview: Supports the scientific community in an effort to redefine tumor classifications using molecular rather than morphological criteria.

- Research Categories: Biology; Etiology; Prevention; Early Detection, Diagnosis, and Prognosis.
- Relevant Resource Resulting From This Initiative: The Director's Challenge program Web site provides researchers with information, analytical tools, and microarray data sets. The Molecular Portraits of Human Breast Tumors microarray data set is available. Between 1998 and 2003, two projects relevant to breast cancer research were supported through RFA-CA-98-027. Specific projects can be found in Appendix B, Tables B2, B29, and B30, by searching for the RFA number.

- Exploratory Grants for Correlative Laboratory Studies and Clinical Trials (PA-98-042)
  - Overview: Supports the development of innovative therapeutic clinical trials or new correlative laboratory studies using patient specimens from therapeutic clinical studies.
  - Research Categories: All.
  - Relevant Research Projects Resulting From This PA: Between 1998 and 2003, 12 projects relevant to breast cancer research were supported through the current PA and the previously issued PAs (PA-96-040 and PA-94-050).[c]
- Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses (FLAIR) (http://dtp.nci.nih.gov/branches/gcob/gcob_web17.html)
  - Overview: Provides a flexible system within the SBIR and STTR programs to support the extensive needs of the complex drug and vaccine discovery and development process, from basic discovery through proof-of-principle demonstration in clinical trials.
  - Research Categories: Biology; Treatment.
  - Relevant Research Projects Resulting From This Initiative: Between 1998 and 2003, 14 projects relevant to breast cancer research were supported. Specific projects can be found in Appendix B, Table B33, by searching for the PA/RFA numbers (PA-01-091, PAR-00-030, and RFA-CA-98-022).
- Improve DNA, RNA and Protein Availability in Fixed Tissue (PAR-00-079)
  - Overview: Supports the development of improved methods for fixing tissues and making nucleic acids and proteins more readily accessible from archived specimens.
  - Research Categories: Biology; Etiology; Early Detection, Diagnosis, and Prognosis.
  - Relevant Research Project Resulting From This PA: Between 1998 and 2003, two projects relevant to breast cancer research were supported. Specific projects can be found in Appendix B, Tables B2, B13, and B32, by searching for the PA number.
- *In Vivo* Cellular and Molecular Imaging Centers (ICMICs) (http://www3.cancer.gov/bip/ICMICs.htm)
  - Overview: Facilitate interaction among scientists from a variety of fields to conduct multidisciplinary research on cellular and molecular imaging related to cancer.
  - Research Categories: Biology; Prevention; Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Resource Resulting From This Initiative: The NCI is currently supporting 7 ICMIC center grants and 12 pre-ICMIC planning grants that provide time and funds for investigators and institutions to prepare themselves, organizationally and scientifically, to establish an ICMIC.

c. Lists of projects derived from initiatives can be found on the online Supplement to the Breast Cancer Progress Report: Initiatives Database.

- Integrating Aging and Cancer Research (PA-02-169)
  - Overview: Supports projects that expand the knowledge base on aging and age-related aspects of cancer in older persons. This initiative originated from a workshop entitled Exploring the Role of Cancer Centers for Integrating Aging and Cancer Research, which was organized by the National Institute on Aging and the NCI to provide a forum for leaders in cancer and aging research to express their views on pressing research needs.
  - Research Categories: Biology; Prevention; Early Detection, Diagnosis, and Prognosis; Treatment; Cancer Control, Survivorship, and Outcomes.
  - Relevant Resources Resulting From This PA: Reports from seven working groups address topics in Patterns of Care; Treatment Efficacy and Tolerance; Effects of Comorbidity on Cancer; Prevention, Risk Assessment, and Screening; Psychosocial Issues and Medical Effects; Palliative Care; End-of-Life Care and Pain Relief; and the Biology of Aging and Cancer.
- Interdisciplinary Research Teams for Molecular Target Assessment (RFA-CA-00-001)
  - Overview: Supports the development of methods to assess the effects of interventions directed at specific molecular targets that produce or are associated with the cancer phenotype.
  - Research Categories: Prevention; Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Research Projects Resulting From This RFA: Between 1998 and 2003, two projects relevant to breast cancer research were supported through this RFA.[d]
- Minority-Based Community Clinical Oncology Program (MBCCOP) (http://www3.cancer.gov/prevention/ccop/mbccop.html)
  - Overview: Supports a comprehensive clinical trials mechanism for disseminating the latest cancer prevention and treatment research findings to communities with large minority patient populations.
  - Research Categories: Prevention; Treatment; Cancer Control, Survivorship, and Outcomes.
  - Relevant Program Resulting From This Initiative: The MBCCOP is composed of 13 funded groups of hospitals or private practices that participate in NCI-funded clinical trials.
- Minority Institution/Cancer Center Partnership (MI/CCP) (http://minorityopportunities.nci.nih.gov/institutions/)
  - Overview: Supports partnerships between Minority-Serving Institutions and NCI-designated Cancer Centers to increase training and involvement of scientists at minority institutions and to develop collaborative projects that address the disproportionate incidence and mortality rates of cancer in minority populations.
  - Research Categories: All.
  - Relevant Program Resulting From This Initiative: The MI/CCP emphasizes four target areas, including cancer research, research training and career development, cancer education, and cancer outreach. The MI/CCP offers three mechanisms of support for grantees:

    Planning Grant for Minority-Institution/Cancer Center Collaborations (P20)

    Cooperative Planning Grant for Comprehensive Minority Institution/Cancer Center Partnership (U56)

    Comprehensive Minority Institution/Cancer Center Partnership (U54)

d. Lists of projects derived from initiatives can be found in the online Supplement to the Breast Cancer Progress Report: Initiatives Database.

- Molecular Target Drug Discovery for Cancer (PAR-01-045; PAR-01-046)
  - Overview: Supports the identification of novel molecular targets, the validation of the target as a basis for cancer drug discovery, or the development of assays for target function.
  - Research Categories: Biology; Etiology; Prevention; Treatment.
  - Relevant Research Projects Resulting From These PAs: Between 1998 and 2003, 18 projects relevant to breast cancer research were supported. Specific projects can be found in Appendix B, Tables B2, B5, B7, B9, B15, B17, B21, B30, B33, B36, and B29, by searching for the current PA numbers and the previously issued PA/RFA numbers (PAR-00-060, PAR-00-061, PAR-00-062, and RFA-CA-00-002).
- Mouse Models of Human Cancers Consortium (RFA-CA-04-002)
  - Overview: Aims to derive, characterize, and validate mouse strains that model human cancers, including breast cancer, and to make these strains available to the research community. The Consortium infrastructure includes a Breast Cancer Models Working Group that fosters the development and use of mouse models serving as surrogate systems to study human breast cancer. Members of the Working Group are drawn from other NCI networks and consortia and the breast cancer research community, with participation by the Department of Defense and National Institute of Diabetes and Digestive and Kidney Diseases. The MMHCC convenes biannual meetings on progress in breast cancer modeling.
  - Research Categories: Biology; Etiology; Prevention.
  - Relevant Resources Resulting From This Initiative: Through the eMice Web site, researchers have access to mouse strains, reagents, analytical tools, protocols, gene data, drug databases, and other useful resources. There are 13 strains of mice that model breast cancer or breast cancer metastasis that can be ordered from the NCI Mouse Repository for use in research.
- NCI Center for Bioinformatics (NCICB) (http://ncicb.nci.nih.gov)
  - Overview: Provides bioinformatics support and integrates diverse research initiatives.
  - Research Categories: All.
  - Relevant Resources Resulting From This Initiative: NCICB's caCORE information management system software is available to researchers to facilitate their research needs. In 2003, NCICB introduced caBIG as an open-source public bioinformatics platform.
- Nonmammalian Organisms as Models for Anticancer Drug Discovery (PAR-99-019; PAR-99-020)
  - Overview: Supports projects that identify key genes, enzymatic activities, components of signaling pathways, or cellular processes that are altered in human cancer as potential intervention points that could be used in the design of new cancer drugs.
  - Research Categories: Biology; Treatment.
  - Relevant Research Projects Resulting From This PA: Between 1998 and 2003, two projects relevant to breast cancer research were supported.[e]
- Program for the Assessment of Clinical Cancer Tests (PACCT) (http://www.cancerdiagnosis.nci.nih.gov/assessment)
  - Overview: Supports efforts to maximize the impact of cancer treatments and ensures the translation of new knowledge about cancer into clinical practice. A PACCT Strategy Group was convened to develop criteria for assessing which markers are ready for further development.

e. Lists of projects derived from initiatives can be found on the online Supplement to the Breast Cancer Progress Report: Initiatives Database.

- Research Categories: Early Detection, Diagnosis, and Prognosis; Treatment.
- Relevant Programs Resulting From This Initiative: Several Web sites that help researchers gain access to human specimens: NCI Specimen Resource Locator, Shared Pathology Informatics Network, Tissue Array Research Program, and Tissue Expediter.

- Shared Pathology Informatics Network (SPIN) (http://spin.nci.nih.gov/)
  - Overview: Supports efforts to develop and use state-of-the-art informatics techniques to establish an Internet-based virtual database that will allow investigators from multiple institutions to locate appropriate human tissue specimens for their research.
  - Research Categories: Biology; Etiology; Prevention; Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Program Resulting From This Initiative: Software supplied by the SPIN initiative can be run at participating institutions and will be able to respond to researcher-initiated queries with a listing of pathology specimens and related data that meet the query criteria.
- Shared Resources for Scientists Outside NCI Cancer Centers (PAR-99-127)
  - Overview: Provides additional shared resource support to institutions that do not have NCI-funded Cancer Centers or Cancer Center planning grants.
  - Research Categories: Biology; Etiology; Prevention; Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Programs Resulting From This PA: Between 1998 and 2003, seven projects relevant to breast cancer research were supported. Specific projects can be found in Appendix B, Table B33, by searching for the current PA number and the previously issued PA/RFA numbers (PAR-98-092 and RFA-CA-01-020).
- Small Animal Imaging Resource Program (SAIRP) (http://www3.cancer.gov/dip/sairp.htm)
  - Overview: Supports shared imaging resources to be used by cancer investigators and research related to small animal imaging technology.
  - Research Categories: Biology; Etiology; Prevention; Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Research Programs Resulting From This Initiative: Ten participating institutions provide imaging resources for investigators in their region of the United States.
- Small Grants Program for Cancer Epidemiology (http://epi.grants.cancer.gov/ResPort/grants.html)
  - Overview: Supports the formation of relationships between large research institutions and community-based programs and addresses cancer burden in minority communities.
  - Research Categories: Biology; Etiology; Early Detection, Diagnosis, and Prognosis; Treatment; Cancer Control, Survivorship, and Outcomes.
  - Relevant Programs Resulting From This Initiative: Between 1998 and 2003, 53 projects relevant to breast cancer research were supported. Specific projects can be found in Appendix B, Tables B1, B7, B8, B10, and B11, by searching for the PA numbers (PAR-03-010, PA-01-021, PAR-98-023 and PAR-95-077).
- Southern Community Cohort Study (SCCS) (http://www.southerncommunitystudy.org)
  - Overview: Supports a large population-based research study that is examining the reasons African Americans are more likely to be affected by many cancers, including breast cancer.
  - Research Categories: Etiology; Prevention; Cancer Control, Survivorship, and Outcomes.

- Relevant Details of This Study: The SCCS will recruit about 70,000 African-American and 35,000 non-African-American residents of the southern United States who will complete an interview and provide a DNA sample. Health outcomes in this group will be monitored for decades with the goal of identifying genetic factors that predispose certain groups to cancer.

- Special Populations Networks (SPNs) (http://crchd.nci.nih.gov/spn/index.html)
  - Overview: Supports collaborations between large research institutions and community-based programs to find ways of addressing important questions about the burden of cancer in minority communities.
  - Research Categories: Prevention; Treatment; Cancer Control, Survivorship, and Outcomes.
  - Relevant Programs Resulting From This Initiative: The current SPNs are composed of the following 18 projects in 15 states across the United States:

    American Indian Initiative in Arizona

    Appalachia Cancer Network (ACN)

    Arkansas Special Populations Access Network (ASPAN)

    Asian American Network for Cancer Awareness, Research, and Training (AANCART)

    Asian Tobacco Education and Cancer Awareness Research Initiative (ATECAR)

    Cancer Awareness Network for Immigrant Minority Populations (CANIMP)

    Deep South Network for Cancer Control

    East Harlem Partnership for Cancer Awareness

    Imi Halé, the Native Hawaiian Cancer Research and Training Network

    Increasing Access to Clinical and Educational Studies (ACES)

    Latin American Cancer Research Coalition (LACRC)

    Latino/a Research and Policy Center

    Maryland Special Populations Cancer Network

    National Black Leadership-Cancer Control, Research and Training Network (NBL-CCRTN)

    Pacific Islander Cancer Control Network (PICCN)

    Redes En Acción

    Special Populations Network for Cancer Control (SPNCC)

    The Network for Cancer Control Research among American Indian and Alaska Native (AI/AN) Populations.

- Specimen Resource Locator (http://pluto3.nci.nih.gov/tissue/default.htm)
  - Overview: Enables researchers to locate human specimens for cancer research.
  - Research Categories: Biology; Etiology; Prevention; Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Program Resulting From This Initiative: The Specimen Resource Locator Web site provides investigators with information and automated tools for identifying tissue procurement systems, including those with samples from normal and diseased breasts.

- Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors (RFA-CA-01-011)
  - Overview: Supports the development of innovative technologies for the sensitive quantitation of the comprehensive spectrum of proteins present in human tissues.
  - Research Categories: Biology; Early Detection, Diagnosis, and Prognosis.
  - Relevant Research Project Resulting From This RFA: Between 1998 and 2003, one project relevant to breast cancer research was supported through this RFA:

    Technology for Global and Quantitative Proteome Analysis
- Therapeutic Modulation of Angiogenesis in Disease (PAR-98-096)
  - Overview: Encourages the translation of basic knowledge of the angiogenic process into therapeutic applications.
  - Research Categories: Biology; Prevention; Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Research Projects Resulting From This PA: Between 1998 and 2003, six projects relevant to breast cancer research were supported. Specific projects can be found in Appendix B, Tables B3, B15, and B16, by searching for the PA number.
- Unconventional Innovations Program (UIP) (http://otir.cancer.gov/tech/uip.html)
  - Overview: Supports the development of radically new technologies in cancer care that can transform what is now impossible into the realm of the possible for detecting, diagnosing, and intervening in cancer at its earliest stages of development.
  - Research Categories: Early Detection, Diagnosis, and Prognosis; Treatment.
  - Relevant Research Projects Resulting From This Initiative: A list of UIP-funded projects is available online and includes four projects with breast cancer relevance:

    Molecular Imaging and Therapy of Solid Tumors With a Novel $\alpha v\beta 3$-specific Nuclear Nanoparticle Targeted to the Neovasculature

    Novel Technologies for Noninvasive Detection, Diagnosis, and Treatment of Cancer (a)

    Novel Technologies for Noninvasive Detection, Diagnosis, and Treatment of Cancer (b)

    Tissue Perfusion Imaging for Cancer Detection

Specialized Programs of Research Excellence (SPOREs)

In 1992, the NCI established the Specialized Programs of Research Excellence (SPOREs) to promote interdisciplinary research and to speed the bidirectional exchange of information between basic and clinical scientists. The SPORE program facilitates the translation of novel research ideas to the clinical care setting, with the goals of reducing cancer incidence and mortality, improving survival, and improving quality of life. Laboratory and clinical scientists work collaboratively to plan, design, and implement research programs that impact cancer prevention, detection, diagnosis, treatment, and control. In 2002 and 2003, 32 clinical trials in breast cancer research were supported through the Breast Cancer SPOREs. Table 2-2 provides more information on the research projects, core resources, and training and other opportunities that are provided by the current Breast Cancer SPOREs.

Table 2-2. Breast SPOREs

Baylor College of Medicine

Projects:

- Genetic Expression Profile of Taxotere Versus AC Sensitivity
- Growth Factor and Stress Response Pathway in Endocrine Therapy Resistance
- Molecular Classification and Prognostic Profiling of Ductal Carcinoma *In Situ*
- Prevention of Breast Cancer Using Signal Transduction Inhibitors
- Role of High-Frequency Hypersensitive Estrogen Receptor-Alpha Mutation in Breast Cancer Metastasis

Cores: Administrative Core, Biostatistics and Data Management, Pathology Core, and Tissue Core

Additional: Developmental Research Program and Career Development Program

Dana-Farber Cancer Institute

Projects:

- Creation of Animal Models for Human Breast Cancer
- Functional Testing for BRCA1 and BRCA2
- Identification of Targets for Intervention in Breast Cancer
- Molecular Markers in DCIS
- Plasma Estrogens in Breast Cancer Risk and Prevention
- Role of G2 Checkpoint Genes in Breast Cancer Susceptibility

Cores: Biostatistics Core, Clinical Data and Data Management Core, High-Risk Patients and Their Families, and Tissue and Pathology Core

Additional: Developmental Research Program and Career Development Program

Duke University Medical Center

Projects:

- Application of Pharmacogenomics to Treatment of Breast Cancer
- Genetic Modifiers of BRCA1 and BRCA2
- Hypoxia and Chemoresistance in Breast Cancer
- T-Helper Responses to Her2/*neu* in Breast Cancer Patients

Cores: Administration, Tissue Bank, Biostatistics and Informatics, and Molecular and Cell Technology

Additional: Developmental Research Program and Career Development Program

Georgetown University Medical Center

Projects:

- A Phase III Multicenter Randomized Trial Comparing Cyclophosphamide, Thiotepa, and Carboplatin (STAMP V) With or Without IL-2-Activated Stem Cell Transplantation and Parenteral IL-2 for High-Risk Breast Cancer Patients
- Antimetalloprotease Therapy
- Development of Her-2/*neu*-Targeted Small Molecule Inhibitors as Novel Cancer Therapeutics
- Inhibition of Breast Cancer Xenograft Tumor Growth by a Naturally Existing Secreted Form of VEGI (Vascular Endothelial Growth Inhibitor)
- Mammary Carcinogenesis, the Role of Pleiotrophin
- Resistance to Hormone and Chemotherapy in Breast Cancer
- Systemic *p53* Gene Therapy Markedly Enhances the Efficacy of Conventional Cancer Therapies

Cores: Breast Cancer Cell Line Resource, Breast Cancer Tumor Bank, SPORE Clinical Research Core, The Breast Cancer Serum Biomarker Resource, and Transgenic Shared Resource Core

Additional: Developmental Research Program and Career Development Program

Northwestern University Medical School

Projects:

- Actions of Estrogen Agonists and Antagonists by Nonclassical Transcription Pathways
- An Angiostatic Cocktail for Women With Refractory Breast Cancer: A Translational Study
- Antiestrogens and Breast Density in Premenopausal Women
- Drug Resistance to Antiestrogens

Cores: Administrative Core, Biostatistical Core, Clinical Core, and Tissue Resource Core

Additional: Developmental Research Program and Career Development Program

The Johns Hopkins University School of Medicine

Projects:

- Molecular Detection of Breast Cancer
- Molecular Epidemiology of Progression to Breast Cancer
- Molecular Markers for Breast Cancer
- Molecular Phenotypes of Breast Cancer
- Novel Polyamine Analogues for Breast Cancer Treatment
- Use of Modulators of DNA Methylation and Histone Deacetylation to Treat Breast Cancer
- Vaccines: A New Paradigm for Breast Cancer

Cores: Administration and Communication Core, Biostatistics and Bioinformatics Core, and Human Specimen Resource and Database

Additional: Developmental Research Program and Career Development Program

University of Alabama at Birmingham

Projects:

- Biology and Intermediate Marker Role of a Novel Breast Cancer Oncogene, GKLF
- Gene Therapy Specifically Directed at Tumor Vasculature
- Molecular Regulation of Breast Cancer Metastasis
- Polynucleotide Vaccine Therapy of Breast Cancer
- Preclinical/Clinical Development of Novel Retinoids
- Pretargeting Radioimmunotherapy of Metastatic Breast Cancer

Cores: Administrative Core, Biostatistical Core, Tissue Procurement Core, Immunopathology Core, and Clinical Trials Core

Additional: Developmental Research Program and Career Development Program

University of California, San Francisco

Projects:

- A New Model System to Identify Markers for Risk and Targets for Chemoprevention
- Breast Cancer Therapeutic Agents That Force Telomerase Misfunction
- Identification and Targeting of Novel Breast Cancer Antigens for Antibody-Based Breast Cancer Therapy
- Molecular Determinants of Response to RTK Pathway Inhibitors
- Predictors of Recurrence in Women with DCIS
- Targeted Drug Delivery via Immunoliposome Technology

Cores: Administrative Core, Advocacy Core, Preclinical Animal Core, and Tissue-Outcomes Core

Additional: Developmental Research Program and Career Development Program

University of North Carolina at Chapel Hill

Projects:

- A Novel Chemotherapy Combination for Breast Cancer
- Breast Tumor Molecular "Profiling" Using cDNA Microarrays
- Carolina Breast Cancer Study: DNA Repair Genes and Breast Cancer Risk
- Carolina Breast Cancer Study: ER Alterations in Breast Cancer Development
- Correlation of Molecular Markers With Response to Neoadjuvant Chemotherapy
- Enhancing a Breast Cancer Vaccine
- Inhibition of Chemotherapy-Induced NF B

Cores: Administrative Core, Biostatistics and Bioinformatics Core, Genomics and Microarray Core, Molecular Analysis and High-Throughput Genotyping Core, and Tissue Procurement and Analysis Core

Additional: Developmental Research Program and Career Development Program

Vanderbilt University

Projects:

- HER (erbB) Tyrosine Kinase Inhibitors in Treatment-Naïve, Operable Breast Cancer
- Molecular Epidemiology of Proliferative Breast Disease
- Molecular Imaging of Breast Carcinoma and Therapeutic Response
- Predictive Markers of Clinical Response to Paclitaxel Therapy in Stage II/III Breast Cancer

Cores: Administrative Core, Antibody Production and Characterization Core, Biomedical Informatics Core, Biostatistics Core, Proteomics and Emerging Technologies Core, and Tissue Core

Additional: Developmental Research Program and Career Development Program

Ongoing NCI Research: SPOREs

Developmental Projects in Early Detection and Drug Targeting

The SPORE Working Group on Biomarker Development recognizes the importance of pursuing research on novel biomarkers for potential clinical applications. This group recently identified the *KLF4 Biomarker Project,* currently under way at the University of Alabama (UAB), as an important area for future development. Researchers involved with this project are testing the hypothesis that nuclear localization of the Krüppel-like transcription factor (KLF4) protein identifies an aggressive subset of early-stage breast cancers. Previous studies have demonstrated that KLF4 is upregulated in breast cancer and squamous cell carcinomas of the oral cavity and skin (Foster et al., 2000). In their first study of 146 patients, researchers demonstrated that the KLF4 marker is an independent prognostic factor that is more strongly associated with an outcome than any other biomarker assessed in parallel (p53, ER/PR, p27Kip1, EGFR, Ki67, Bcl-2, and Her2/*neu*) (Pandya et al., 2004). Results from this initial study suggest that KLF4 could be used to identify approximately one-half of early-stage breast cancer patients who will eventually die of the disease.

The SPORE Molecular Targets Working Group identified the *Immunoliposome Project* at the University of California, San Francisco (UCSF) Breast Cancer SPORE site as an important project. Scientists at this site are working on advanced drug delivery technologies that enable highly robust and versatile encapsulation of various cytotoxic compounds into stabilized liposomes. Novel liposome constructs containing existing chemotherapeutic drugs vinorelbine, vincristine, epirubicin, and campothecins result in extremely stable and long-circulating nanoparticles. The antitumor activity of liposome-encapsulated drugs can be enhanced by the addition of an immunoconjugate, which allows for antigen-specific targeting of the liposome. The UCSF Breast Cancer SPORE project has developed immunoliposomes (ILs) directed against HER2 and has demonstrated their effectiveness in delivering doxorubicin for enhanced *in vivo* antitumor activity (Park et al, 2002). HER2-targeted ILs containing doxorubicin have been optimized for clinical development and are currently being manufactured by industry partners for use in clinical studies.

Collaborations and Partnerships

Breast Cancer SPOREs meet annually at a SPORE Investigators Workshop to share data, assess research progress, and identify new research opportunities. In many cases, funded SPORE institutions forge collaborations with each other and with clinical trials groups to increase the likelihood of success for their projects. For example, the University of California, San Francisco Bay Area Cancer Translational Research Program, the University of North Carolina at Chapel Hill Breast Cancer SPORE, and the Georgetown University SPORE share funding to study the use of magnetic resonance imaging (MRI) as a quantitative tool to measure response to chemotherapy in Stage III breast cancer patients and to correlate these findings with biomarker analyses performed on tumor biopsies. The study entitled *Stage III MRI and Correlative Science Companion Study* is led by UCSF and includes collaborations at SPORE institutions, centers that do not have Breast Cancer SPORE funding (the Memorial

Sloan-Kettering Cancer Center, the University of Texas Southwestern Medical Center, and the University of Pennsylvania Cancer Center), and other NCI-sponsored groups (the Cancer and Leukemia Group B [CALGB] and the American College of Radiology Imaging Network [ACRIN]). The SPORE program supports the correlative science component of the project while the MRI analyses and clinical trials are supported by ACRIN and CALGB, respectively. The inclusion of this many collaborating institutions ensures the accrual of sufficient numbers of patients for solid statistical analysis of the study's endpoints, which include the identification of new, early predictors of response and the establishment of a direct relationship between imaging/marker findings and survival.

In another example of a unique collaboration, the Avon Foundation (AVON) and NCI developed the *AVON-NCI Progress for Patients (PFP) Awards Program*, a special private-public partnership to fund innovative research for preventing, detecting, diagnosing, and treating breast cancer. AVON pledged $20 million to fund breast cancer research over 5 years through a limited competition involving institutions with NCI-funded SPORE grants and Cancer Center grants. The program goal is to increase the number of new early-phase clinical breast cancer interventions and help move promising drugs, biomarkers, and procedures into Phase III clinical trials. By the end of 2003, eight SPORE projects in breast cancer had received supplemental funding through the PFP Awards mechanism. The following ongoing research projects address issues relevant to breast cancer prevention, treatment, and early detection/diagnosis/prognosis:

- Antiangiogenic Therapies for Breast Cancer
- Biological Markers in Breast Cancer Treated by Neoadjuvant Chemotherapy
- Markers of Short-Term Breast Cancer Risk in Fine-Needle Aspiration
- New Biomarkers for Aromatase Inhibitor Therapy
- Novel Approaches for Patients With Large Breast Cancers
- Response to Preoperative Therapy in Breast Cancer
- Surrogate Endpoints in Prevention Studies and Ductal Lavage
- Validation of Breast Biomarker Panel

These types of collaborations and partnerships increase the likelihood of success for SPORE researchers in their efforts to translate basic laboratory findings into practical clinical applications for treating breast cancer.

NCI-Supported Research Referenced in Chapter 2

Foster KW, Frost AR, McKie-Bell P, Lin CY, Engler JA, Grizzle WE, Ruppert JM. Increase of GKLF messenger RNA and protein expression during progression of breast cancer. Cancer Res. 2000 Nov 15;60(22):6488-6495.

Pandya AY, Talley LI, Frost AR, Fitzgerald TJ, Trivedi V, Chakravarthy M, Chhieng DC, Grizzle WE, Engler JA, Krontiras H, Bland KI, LoBuglio AF, Lobo-Ruppert SM, Ruppert JM. Nuclear localization of KLF4 is associated with an aggressive phenotype in early-stage breast cancer. Clin Cancer Res. 2004 Apr 15;10(8):2709-2719.

Park JW, Hong K, Kirpotin DB, Colbern G, Shalaby R, Baselga J, Shao Y, Nielsen UB, Marks JD, Moore D, Papahadjopoulos D, Benz CC. Anti-HER2 immunoliposomes: Enhanced efficacy attributable to targeted delivery. Clin Cancer Res. 2002 Apr;8(4):1172-1181.

Chapter 3:
Breast Cancer Biology: NCI's Investment and Recent Progress

Given that the two clinical challenges in breast cancer research are to prevent the onset of disease and to effectively treat metastatic disease, the overarching basic biological questions that need to be answered involve understanding the normal and early malignant biology of the mammary gland, and identifying factors responsible for metastatic disease. *Charting the Course: Priorities for Breast Cancer Research*

Basic biology research is fundamentally important for the advancement of many areas of cancer research, as it provides the foundation on which applied studies in early detection, diagnosis, prevention, and treatment are built. In its 1998 report, the Breast Cancer PRG outlined three overarching themes in breast cancer biology research that required specific attention in the coming years: the need to elucidate the normal biology of the mammary gland, the process of malignant transformation in the breast, and mechanisms of breast cancer metastasis. Within these three priority areas, the PRG identified more than 20 subpriorities that could be used to guide the research community in its efforts to understand the basic biology of breast cancer.

In the years since the PRG report, the NCI has generated specific initiatives, Program Announcements and Requests for Applications aimed at addressing the PRG's priorities. Research conducted in response to these efforts, in addition to the broad range of investigator-initiated biology research, has been fruitful, yielding results in breast cancer biology that have fueled progress in other areas of breast cancer research. Significant progress has been made in understanding the biology of mammary stem cells, genetic changes that occur during breast cancer development and metastasis, mechanisms by which tumor-suppressor genes (e.g., BRCA1 and BRCA2) function, and nuclear hormone receptor function.

New mouse models of breast cancer have been generated that closely mimic the different types of breast cancer found in humans. Models such as the BRCA1-null mouse and the Her2/*neu* transgenic mouse have been useful for understanding the biology of estrogen receptor (ER)-negative breast tumors, which are the most difficult to treat.

The information gleaned from these and other biology projects have contributed to progress in the areas of breast cancer prevention, detection, diagnosis, and treatment. For a more comprehensive understanding of this progress, readers are urged to see Chapters 5, 6, and 7 of this report. In addition, basic biology research both influences and is influenced by etiologic research on genetics and biological mechanisms of cancer development and progression. Examples of progress can be found in this chapter and Chapter 4.

NCI's Investment and Response

From FY1998 to 2003, NCI's extramural investment in research on breast cancer biology has increased from $43.2 million to $86 million (Figure 3-1). This increase in funding corresponds to increases in the number of projects that are responsive to PRG priorities in biology. Table 3-1 summarizes the NCI's responsiveness to the three Breast Cancer PRG research priorities for biology and the genetics priorities relevant to biology.[1]

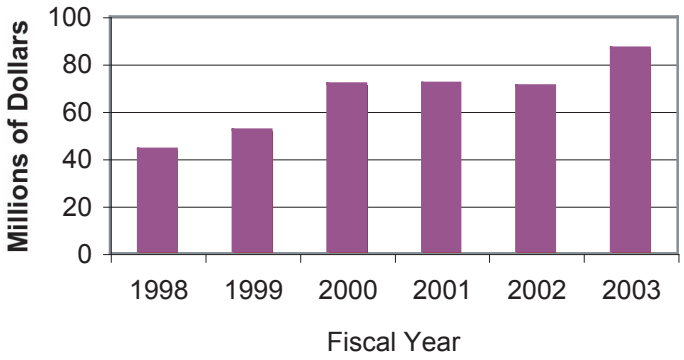


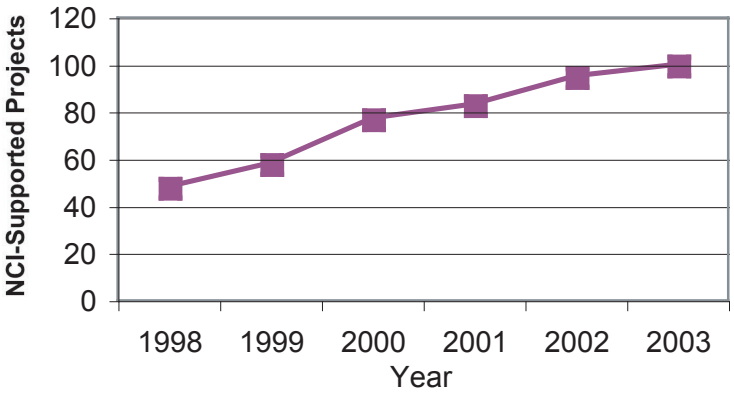
Figure 3-1. NCI's extramural investment in breast cancer biology research: 1998-2003 (in millions of dollars)

1 A project may map to more than one PRG priority and therefore be represented in more than one figure. Projects active in 2003 are listed in Appendix B (Tables B-1 to B-6) by the Principal Investigator's name for each PRG priority.

Table 3-1. NCI Efforts Responsive to PRG Priorities and Opportunities in Biology[a]

PRG Priority:

What are the genetic and biological bases of mammary gland development throughout the life of the organism?[b]



NCI Efforts:

- The original PRG indicated six subpriorities to this priority, which addressed the following topics:
  - The nature of mammary gland stem cells
  - Principal cell types involved in mammary development
  - Control of growth, death, and differentiation during mammary development
  - Critical transcriptional regulatory mechanisms in mammary development, including steroid receptor coactivators and corepressors
  - Principal signaling molecules and pathways in mammary gland development
  - Principal cell cycle checkpoints and their controls in mammary development
- In FY2003, examples of active areas of investigation included vitamin D-mediated apoptosis in mammary cells, prolactin interactions in mammary gland development and tumorigenesis, biology of mammary gland development and tumorigenesis, and *in vivo* cell growth control mediated by C/EBP-β and C/EBP-delta.
- On October 2-3, 2002, NCI sponsored a conference on *Laser Capture Microdissection and Macromolecular Analysis of Normal Development and Pathology*. On July 19-20, 2001, NCI sponsored the *Breast Cancer Think Tank: Mammary Gland Biology Seminar Series* to discuss mammary gland biology with the NCI research community.
- NCI initiatives addressing this priority included the Cancer Genome Anatomy Project (CGAP), Complex Formation in Hormonal Regulation of Gene Expression, Cooperative Human Tissue Network (CHTN), and Mammalian Gene Collection.

PRG Priority:

What are the genetic and epigenetic bases of pathologic lesions that occur during the progression of breast cancer from the earliest hyperplasias to invasive disease?[c] (Biology-B)

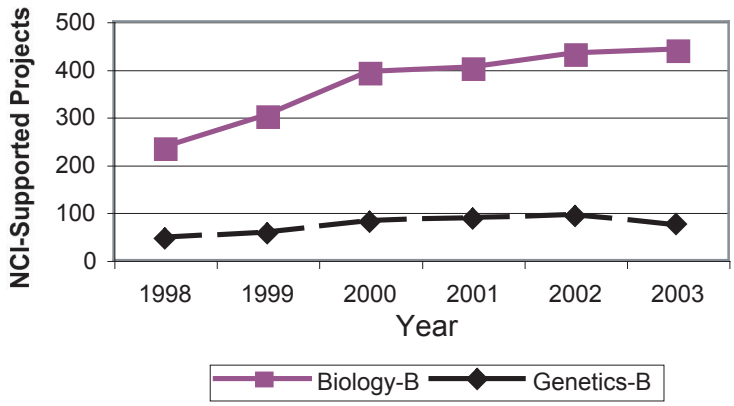
Identify somatic mutations and epigenetic alterations that are due to exogenous factors or to chance. As these are detected, it will be important to know which ones are rate limiting. Once rate-limiting changes are identified, specific pathways altered by these genetic events can provide clues to possible targets for: (1) identifying very small lesions

a. Some of the original PRG priorities are addressed jointly in Table 3-1 because these priorities address partially overlapping issues and they are relevant to many of the same research projects and initiatives.

b. This priority merges the two original PRG priorities: "What are the genetic and biological bases of mammary gland development?" from the Biology section and "Characterize genetic and expression profiles for normal breast epithelium at birth, puberty, adult, pregnancy, lactation, regression, and menopause" from the Genetics section.

c. This priority merges the two original PRG priorities "What are the genetic and epigenetic bases of pathologic lesions that occur during the progression of breast cancer from the earliest hyperplasias to invasive disease; can we develop appropriate diagnostic markers based on these studies?" from the Biology section and "Characterize genetic and expression profiles of breast abnormalities at progressive stages of development from normal to invasive disease" from the Genetics section.

(diagnosis); (2) treatment (by reversing the altered phenotype); (3) identifying tumor cells (to individualize therapy based on tumor genotype); and (4) prevention (by systemic treatment of women before critical changes occur).[d] (Genetics-B)



NCI Efforts:

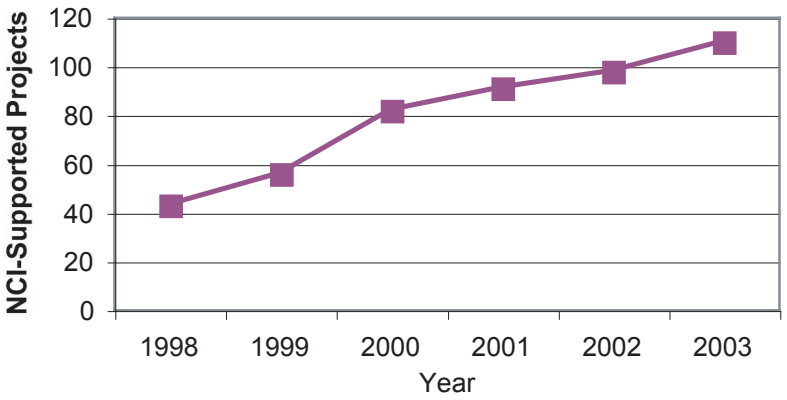
- The original PRG indicated eight subpriorities for the Biology-B priority, which addressed the following topics:
  - Critical signaling pathways in tumor progression
  - The mechanism by which genetic and genomic instabilities are triggered during tumor progression
  - Critical transcriptional regulatory mechanisms in mammary development, including steroid receptor coactivators and corepressors
  - The bases of stem cell-carcinogen interactions
  - Epithelial and stromal cell interactions that are important in tumor cell progression
  - The nature of checkpoint abrogation mechanisms in tumor progression
  - The relative roles of estrogen receptor (ER)-α and ER-β in tumor progression
  - The importance of immune tolerance in tumor progression
- In FY2003, examples of active areas of investigation relevant to the following priorities included:
  - Biology-B: Calmodulin and ER function, role of Her4 as a differentiation factor in breast cancer, role of the tumor suppressor LIBC in inflammatory breast cancer phenotype, the structural basis for ER-β receptor activation, actin-regulated apoptosis in mammary tumorigenesis, molecular alterations in premalignant and *in situ* breast lesions, TGF-β receptor and tumor progression, and identification of allele variant genes that are risk factors for human breast cancer.
  - Genetics-B: Accelerated senescence in tumor cells, a novel HOX gene target in breast cancer, DNA hypermethylation in breast cancer, gene expression signatures of early breast cancer, identification of M5CpG alterations in breast carcinomas, and identification of chromosomal aberrations in human epithelial cancers and hematological malignancies and their respective murine model systems (comparative cancer cytogenetics).
- On October 17-21, 2001, NCI and the American Association for Cancer Research sponsored a special conference, *Cancer and Chromosomal Organization and Epigenetics of Cancer*. On July 19-20, 1999, NCI sponsored the workshop *DES Research Update 1999: Current Knowledge, Future Directions* to address the status of biological, epidemiological, clinical, and education/outreach research on diethylstilbestrol (DES).

NCI initiatives addressing this priority included Applications of Innovative Technologies for the Molecular Analysis of Cancer, Cancer Molecular Analysis Project (CMAP), Cooperative Human Tissue Network (CHTN), Cooperative Breast Cancer Tissue Resource (CBCTR), Director's Challenge: Toward a Molecular Classification of Tumors, and Mouse Models of Human Cancers Consortium.

d. This priority was part of the Genetics section in the original Breast Cancer PRG report.

PRG Priority:

What are the molecular, genetic, and cellular bases of the biological processes involved in metastasis? Can we develop appropriate diagnostic markers based on these studies?

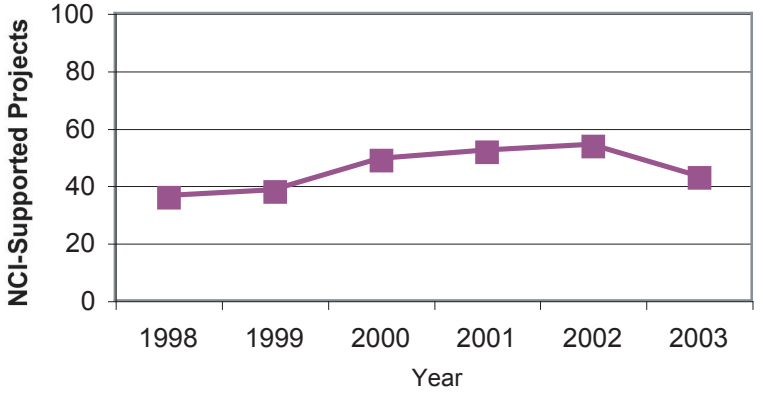


NCI Efforts:

- The original PRG indicated nine subpriorities to this priority, which addressed the following topics:
  - Cell survival pathways operant in metastasis
  - Regulation of tumor angiogenesis
  - Interaction of metastatic cells with bone
  - Control of proteolysis in metastasis
  - Tumor cell motility mechanisms operant in metastasis
  - Importance of epithelial-stromal interactions in metastasis
  - Important signaling pathways in metastasis
  - Cell-cycle checkpoint abrogation mechanisms operant in metastatic cancers that render them more refractory to systemic treatment
  - Aspects of tumor cell physiology of established and metastatic cancers that render them more refractory to systemic treatments
- In FY2003, examples of active areas of investigation included antiestrogenic effects on tumor angiogenesis, a novel function for vascular epithelial growth factor (VEGF) in breast carcinoma survival, biology of VEGFs in the mammary gland, molecular mechanism of tumor-osteoclast interactions, imaging lymphatic clearance in tumor metastasis, effect of obesity on mammary tumorigenesis and metastasis, molecular analysis of breast cancer metastasis to the brain, and molecular biology of the metastatic phenotype.
- On April 25-27, 2002, NCI sponsored the *3rd North American Symposium on Skeletal Complications of Malignancy*.
- NCI initiatives addressing this priority included The Director's Challenge: Toward a Molecular Classification of Tumors, Molecular and Cellular Biology of Metastatic Tumor Cells, Mouse Models of Human Cancers Consortium, and Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors.

PRG Priority:

Identify and clone the remaining major predisposing genes.[e]



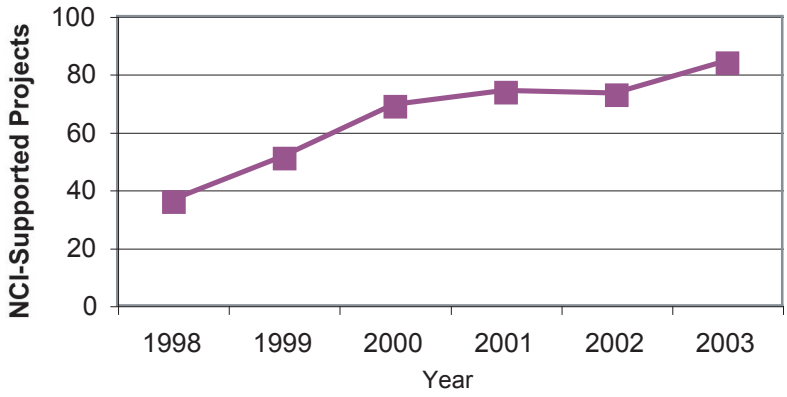
e. This priority was part of the Genetics section in the original Breast Cancer PRG report.

NCI Efforts:

- In FY2003, examples of active areas of investigation included functional analysis of BRCA1, Protein Kinase C as a marker in tamoxifen-resistant breast cancer, the genetics and epigenetics of cancer, identification of allele variant genes that are risk factors for human breast cancer, and the interaction of genes with risk behaviors such as smoking in breast cancer etiology.
- NCI initiatives addressing this priority included the Cancer Genome Anatomy Project (CGAP), Mammalian Gene Collection, and Specimen Resource Locator.

PRG Priority:

Use experimental model systems to determine the effects of mutant genes on the mammary gland, ovary, and endometrium.[f]



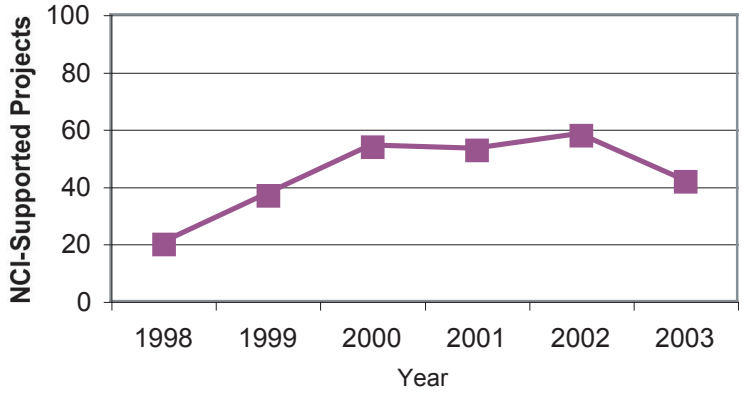
NCI Efforts:

- In FY2003, examples of active areas of investigation included use of an ER-negative transgenic rat mammary model overexpressing *neu* to study chemoprevention; transgenic models for prostate and breast cancer; functional analysis of breast cancer susceptibility genes in mice; identification of chromosomal aberrations in human epithelial cancers, hematological malignancies, and their respective murine model systems; and genetic modifiers of initiation and progression of mammary cancer.
- NCI initiatives addressing this priority included the Molecular and Cellular Biology of Metastatic Tumor Cells, Mouse Models of Human Cancers Consortium, and Stages of Breast Development: Normal to Metastatic Disease.

Additional Breast Cancer Biology Projects:

NCI Efforts:

- In FY2003, examples of active areas of investigation included the role of the prohibitin protein in mediating breast cancer suppression; the Cooperative Breast Cancer Tissue Resource; function of steroid receptors in subcellular compartments; *in vivo* imaging analysis of steroid/nuclear receptor function, tumor oxygenation, vascularization, and radio response; regulation of the sodium/iodide symporter in the breast; and structure of mammary tumor MAT8 and the FXYD proteins.



f. This priority was part of the Genetics section in the original Breast Cancer PRG report and modified from the original "Carry out experimental human genetics in mice, by generating mice with both wild-type and mutant human genes. Determine the effects of these genes on mammary gland, ovary, and endometrium (recognizing mouse-human differences). Determine the effects of mutations against different genetic backgrounds, with the goal of identifying genetic modifiers of mutant alleles."

The NCI has responded to the PRG priorities and recommendations in breast cancer biology by expanding its investment in initiatives relevant to this specific research category. Initiatives that directly impacted breast cancer biology research during the years 1998 to 2003 are described in Table 3-2. In addition to these category-specific initiatives, some initiatives are relevant to many aspects of breast cancer research, including biology. The following list of broadly applicable initiatives is described in detail in Table 2-1:

- Aging Women and Breast Cancer
- Applications of Innovative Technologies for the Molecular Analysis of Cancer
- Bioengineering Research Partnerships
- Breast Cancer Faculty
- Cancer Biomedical Informatics Grid (caBIG)
- Cancer Centers Program
- Cancer Genome Anatomy Project (CGAP)
- Cancer Imaging Program (CIP)
- Cancer Molecular Analysis Project (CMAP)
- Cancer Research Small Grant Program
- Cancer Research Training, Career Development, and Education Opportunities
- Competing Supplements for Organotypic Models of Cancer
- Cooperative Breast Cancer Tissue Resource (CBCTR)
- Cooperative Human Tissue Network (CHTN)
- Director's Challenge: Toward a Molecular Classification of Tumors
- Exploratory Grants for Correlative Laboratory Studies and Clinical Trials
- Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses (FLAIR)
- Improving DNA, RNA, and Protein Availability in Fixed Tissue
- Insight Awards to Stamp Out Breast Cancer
- Integrating Aging and Cancer Research
- *In Vivo* Cellular and Molecular Imaging Centers (ICMICs)
- Minority Institution/Cancer Center Partnership (MI/CCP)
- Molecular Target Drug Discovery for Cancer
- Mouse Models of Human Cancers Consortium
- NCI Center for Bioinformatics
- Nonmammalian Organisms as Models for Anticancer Drug Discovery
- Shared Pathology Informatics Network (SPIN)
- Shared Resources for Scientists Outside NCI Cancer Centers
- Small Animal Imaging Resource Program (SAIRP)
- Small Grants Program for Cancer Epidemiology

- Specialized Programs of Research Excellence (SPOREs) in Breast Cancer
- Specimen Resource Locator
- Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors
- Therapeutic Modulation of Angiogenesis in Disease

Table 3-2. NCI Initiatives Relevant to Breast Cancer Research: Biology[a]

Initiatives Focused on Breast Cancer Research

- Stages of Breast Development: Normal to Metastatic Disease (PA-99-162)
  - Overview: Supports the study of the molecular, cellular, endocrine, and other physiological influences on the development and maturation of the normal mammary gland and alterations involved in early malignant and metastatic breast cancer.
  - Relevant Projects Resulting From This PA: Between 1998 and 2003, 25 projects relevant to breast cancer research were supported through this PA. Specific projects can be found in Appendix B, Tables B1-B5, B7, B9, B11, B14, B19, B30, and B33, by searching for the PA number.

Initiatives With Breast Cancer-Relevant Components

- Bioengineering Nanotechnology Initiative (PA-02-125)
  - Overview: Supports projects on nanotechnology that are potentially useful to biomedicine.
  - Relevant Projects Resulting From This PA: Pending—this PA will remain open until June 3, 2005.
- Complex Formation in Hormonal Regulation of Gene Expression (PA-02-100)
  - Overview: Supports research addressing the role of nuclear hormone receptor complex formation in hormonal regulation of gene expression.
  - Relevant Projects Resulting From This PA: Pending—this PA will remain open until May 1, 2005.
- Mammalian Gene Collection (MGC) (http://mgc.nci.nih.gov/Info/Summary)
  - Overview: A trans-NIH initiative that provides full-length open-reading-frame (FL-ORF) clones for human, mouse, and rat genes.
  - Relevant Results From This Initiative: The MGC has sequenced and verified the complete FL-ORFs for a nonredundant set of 11,666 human genes, 18 of which are breast cancer-specific.
- Molecular and Cellular Biology of Metastatic Tumor Cells (PA-01-020)
  - Objective: Supports the study of molecular and cellular biology of metastatic tumor cells through collaborations that facilitate scientific interchange between investigators with experience in the biology of metastasis and others with more basic scientific disciplines such as molecular biology, cellular biology, andbiochemistry.
  - Relevant Research Projects Resulting From This PA: Between 1998 and 2003, 15 projects relevant to breast cancer research were supported through this PA. Specific projects can be found in Appendix B, Tables B24 and B32, by searching for the current PA number and the previously issued PA numbers (PA-98-029 and PA-93-016).

a. Lists of the projects derived from each initiative can be located in the online Supplement to the Breast Cancer Progress Report: Initiative Database.

- Molecular Interactions Between Tumor Cells and Bone (RFA-CA-03-013)
  - Overview: Supports studies that delineate the role of bone microenvironment on tumor cell survival and colonization. Collaborative interactions among bone biologists, clinical oncologists, and cancer biologists are highly encouraged. These studies contribute toward a better understanding of the molecular events that account for homing of tumor cells to the bone and lead to the generation of novel therapeutic reagents.
  - Relevant Projects Resulting From This RFA: Between 1998 and 2003, three projects relevant to breast cancer research were supported through this RFA. Specific projects can be found in Appendix B, Tables B3 and B33, by searching for the current RFA number.
- Structural Biology of Membrane Proteins (PA-02-108 , PA-02-060)
  - Overview: Supports research leading to the solution of membrane protein structures at atomic resolution, with specific emphasis on membrane proteins and complexes associated with the biology, diagnosis, and treatment of cancer.
  - Relevant Projects Resulting From These PAs: Between 1998 and 2003, one project relevant to breast cancer research was supported through the previously issued PA (PA-99-004): Structure of Mammary Tumor MAT8 and the FXYD Proteins.

Ongoing NCI Research: Recent Progress in Breast Cancer Biology

Mammary Gland Development and Breast Cancer Susceptibility

NCI-supported studies on the basic biology of breast cancer have led to considerable progress toward defining and characterizing the cells and genes that contribute to breast cancer susceptibility, initiation, and establishment. One especially active area focuses on the question of whether breast cancer heterogeneity results from different cells of origin undergoing discrete and different initiating events, alternate pathways of carcinogenesis from a single kind of cancer progenitor, or a combination—i.e., a limited set of progenitors and several common pathways acting in concert—that results in the heterogeneous tumor types that are observed. The answers from studies in a variety of *in vitro* and *in vivo* human and rodent model systems indicate that breast cancer heterogeneity is due to this last mechanism.

Studies of the hematopoietic system and its malignancies clearly demonstrate that there are stem and progenitor cell populations with differing properties that are targets for oncogenesis. Stem cells in adult tissues are able to divide to renew themselves as well as to differentiate into the cell lineages that are needed for normal function of a particular tissue or organ (Weissman et al., 2001). Mammary gland epithelial stem cells possess a high capacity to reproduce themselves, as well as the developmental ability to produce lineage-committed ductal and alveolar cells in the breast, and recent work established that an entire functional mammary gland can be generated from these stem cells (Kordon and Smith, 1998). Mammary stem cells are thought to be essential for the normal growth and differentiation of the mammary gland during puberty, pregnancy, lactation, and involution. Unlike other adult tissues and organs, which have an established morphology, mammary gland architecture undergoes substantial change during these processes.

During the involution process that follows weaning and cessation of lactation, the majority of mammary alveolar cells undergo apoptosis, with the exception of a unique population of epithelial stem cells that appears to undergo expansion at this time. This expanding population of cells increases in size with each subsequent pregnancy. This distinctive population is not present in the nulliparous mammary gland; thus, these cells are hypothesized to contribute to the tumorigenesis resistance mechanism displayed by multiparous women (Wagner et al., 2002). There are several experimental rodent models that point to the *p53* tumor suppressor as a key player in the process of hormone-induced protection (Medina and Kittrell, 2003; Medina, 2004).

Although the concept of breast cancer stem cells is not new, only recently have researchers identified putative stem cells in the mammary gland and demonstrated their role in the development of breast cancer. In a landmark experiment, these rare breast cancer-initiating cells were identified in a population of human mammary tumor cells injected into immunocompromised mice (Al-Hajj et al., 2003). These transformed stem cells are able to give rise to heterogeneous mammary tumors and likely represent the only known population of tumor cells with the capability of initiating tumor growth. These findings have important therapeutic ramifications and shed light on the mechanism by which the induction of premature stem cell senescence reduces the risk of mammary cancer (Boulanger and Smith, 2001).

One particularly important issue for choice of therapy and long-term prognosis is the stem/progenitor cell origin of the breast tumors that are ERα-negative versus ERα-positive; the former are more aggressive, less responsive to therapy, and far more likely to recur. One hypothesis is that the mammary gland self-renewing stem cell is ERα-negative, and in response to differentiation conditions, ERα-positive progenitors arise that continue to self-replicate or differentiate. The ERα-negative stem cell can also give rise via the same or different mutations to ERα-negative cancer stem cell populations with different properties. Subsequent stochastic changes give rise to a number of subsets of breast cancer with differing degrees of aggressiveness and clinical course (Dontu et al., 2004). These hypotheses will require further testing.

The capacity now exists to test these stem/progenitor questions with a variety of model systems. NCI-funded investigators identified a mammary epithelial cell population with several stem/progenitor cell qualities, including expression of stem cell antigen-1 (Sca-1). These markers are useful for both the isolation of functional mammary epithelial stem/progenitor cells and the analysis of tumor etiology and phenotype in genetically engineered mouse models (Welm et al., 2002). Transgenic expression of the Wnt-1 proto-oncogene in the mouse mammary gland causes expansion of epithelial cells that express progenitor cell markers keratin 6 and Sca-1. The resulting tumors express these markers and contain at least two populations of tumor cells—epithelial cells and myoepithelial cells—which implies that they arose by differentiation from an oncogenic progenitor cell. These results suggest that mammary stem and/or progenitor cells may be targets for oncogenesis by Wnt-1. Mammary tumors arising in transgenic mice that express β-catenin and c-Myc, which both encode proteins in the same pathway as Wnt-1, also have a significant proportion of myoepithelial cells and cells expressing keratin 6; however, mammary tumors from transgenic mice that express *neu*, H-*Ras*, or polyoma middle T-antigen contain very few myoepithelial cells or cells expressing markers of progenitor cells. These data suggest that the heterogeneity of tumors in mouse breast cancer models may partially reflect the selection or expansion of different progenitors (Li, Welm, et al., 2003).

Another model that mimics the natural history of a subset of human breast cancer is a *p53*-null mouse that is made in a particular strain background (BALBc). The *p53*-null normal mammary epithelium is as dependent on estrogen and progesterone for growth as *p53*+ epithelium. However, estrogen and progesterone, singly or together, strongly stimulate mammary gland tumorigenesis only in the *p53*-null mouse (Medina et al., 2003). The hormonally transformed ERα-positive cells are serially transplanted into cleared fat pads of *p53*+ mice. The tumors that grow out are often ERα-negative, and serial transplantation of cells from these tumors in ovariectomized *p53*+ mice leads to the development of aggressive tumors, demonstrating that ovarian hormones are no longer required for tumorigenesis. This model should prove valuable for testing chemopreventive agents against either ERα-negative or ERα-positive tumors. This transplantation model is complemented by a *p53*-mutant transgenic mouse model (Lin et al., 2004) in which the activity of *p53* is lost specifically in the mammary gland. The natural history of mammary cancer in this line simulates the transition from ERα-positive to ERα-negative, and both liver and lung metastases are observed. In addition, genetic alterations that accompany human breast cancer progression, such as amplification of c-Myc and activation of Her2/*neu*/*erb*B2, are also reproduced in this model. Effective models of human breast cancer that address defective BRCA1 or BRCA2 can be found in rodents other than mice. Using a very clever technique to screen through the many progeny resulting from germline mutagenesis, a group of investigators was able to identify rat strains that have mutations specifically in these two susceptibility genes (Zan et al., 2003). The rats are being followed for the development of mammary cancer and possible ovarian epithelial cancer.

Due to the multigenic nature of breast cancer, finding all of the genes involved using human population studies is a daunting task. Particularly challenging is the fact that while most susceptibility genes are common, each one has a low penetrance in the general population, which means that many genes probably contribute to susceptibility or resistance. The use of comparative genomics in model systems is increasingly valuable for finding these cooperating alleles. Two studies have used congenic rats to

refine the location of two of the eight susceptibility regions previously identified (Samuelson et al., 2003; Haag et al., 2003). Further refinement is under way to enable isolation of the relevant genes and evaluation of their role in human breast cancer susceptibility. Another research group used a clever strategy that combines the facile genetics of inbred mice and the growing collection of human and mouse SNPs. They substantially narrowed the location of a common susceptibility locus in mice and then searched through SNPs in the human genes in the corresponding human chromosome location to verify the STK15 gene, which encodes the Aurora kinase, as a low-penetrance susceptibility gene in breast cancer. Subsequent studies have shown that this same allelic variant has a role in other common human epithelial cancers (Ewart-Toland et al., 2003). The Aurora kinases normally function to maintain chromosome integrity; if they are overexpressed, they acquire oncogenic properties, causing centrosome amplification, transformation, and aneuploidy. A recent study showed that overexpression of Aurora A kinase is a very early event in rat mammary carcinogenesis (Goepfert et al., 2002); the consistency of the observation regarding centrosome irregularities in a number of human cancers has prompted the development of an Aurora kinase inhibitor that is now in clinical trials.

A number of publications describe innovative new multicell systems to study the interactions of human breast cancer epithelial cells with other cells in the tissue environment. In one case, hydrated collagen gel was used to support studies of the interactions between myoepithelial cells and luminal epithelial cells, and between tumor cells and peritumoral fibroblasts. From these studies, the researchers concluded that myoepithelial cells figure prominently in the maintenance of the correct polarity of the luminal epithelial cells and that direct contact between breast tumor cells and the surrounding fibroblasts causes induction of metalloproteinases and other novel genes (Gudjonsson et al., 2004). Another type of three-dimensional human cell culture system was used to explore the role of a major signal pathway involving PI3-kinase in polarity and proliferation of breast epithelial cells and their malignant counterparts. The study revealed that there are key events in this pathway that have distinct roles for maintaining tissue polarity and that disruption of these events is key to the emergence of malignancy (Liu et al., 2004).

Genetic and Epigenetic Changes in Breast Cancer Development

Breast cancer resembles most other types of cancer in that multiple genetic or epigenetic events must occur in the target cell before it becomes fully malignant. Elucidation of the factors that contribute to mammary tumorigenesis is the common goal of many NCI-supported researchers.

The BRCA1 tumor-suppressor gene is involved in the cellular response to DNA damage and plays a key role in maintaining genome integrity. Half of all inherited forms of breast cancer contain germline mutations in the BRCA1 gene that ablate its function, and an inherited mutation of BRCA1 confers an 85%-90% certainty of female breast cancer by age 70 (Easton et al., 1995). In addition, a significant proportion of high-grade sporadic breast cancers display reduced levels of BRCA1 mRNA and protein, due in part to promoter hypermethylation, a gene-silencing mechanism that is common in human neoplasia (Wilson et al., 1999; Esteller et al., 2000). Researchers studying the structure and function of the BRCA1 protein have recently identified BRCA1-interacting proteins such as BACH1, BARD1, and RAD51 that implicate the tumor-suppressor protein in a variety of cellular activities, including double-strand DNA break repair and transcription of growth inhibitory genes (Cantor et al., 2001; Chen et al., 1998; Boulton et al., 2004).

Amplification or overexpression of the Her2/*neu* receptor tyrosine kinase occurs in about 30% of human breast and ovarian cancers and is associated with a more aggressive course of disease for reasons that may be related to increased proliferation, vessel formation, and/or invasiveness. A breakthrough for the treatment of Her2/*neu*-overexpressing tumors occurred in 1998 with the approval of a new monoclonal antibody-based drug called Herceptin® (trastuzumab). Addition of trastuzumab to the standard chemotherapy regimen yielded higher response rates, longer time to disease progression, and a 20% reduction in the risk of death in women with metastatic breast cancer (Slamon et al., 2001). A recent study demonstrated that younger women with Her2/*neu*-overexpressing breast cancer had an increased risk of developing a secondary tumor in their contralateral breast compared to women whose primary tumors did not overexpress Her2/*neu* (Li, Malone, et al., 2003). Interestingly, these Her2/*neu*-overexpressing cancer cells are more prone to the tumor-promoting effects of ethanol, which was found to increase tumor invasiveness through activation of Her2/*neu* and its downstream signaling components JNK and p38 MAPK (Ma et al., 2003). In laboratory studies, ERα-positive breast cancers that overexpress Her2/*neu* appear to be less responsive to tamoxifen than are

breast cancers with low Her2/*neu* expression. The mechanism behind that observation is in part due to the expression levels of an ERα coactivator, AIB1. If patients' tumors have high levels of both AIB1 and Her2/*neu* expression, their outcome with tamoxifen therapy is very much worse than for either alone (Osborne et al., 2003).

The role of Her2/*neu* in human cancer and the use of Herceptin® prompted the development of a mouse mammary cancer model based on conditional expression of the *neu* oncogene (Moody et al., 2002). When the oncogene is switched on, the mice rapidly develop multiple invasive tumors that readily metastasize to the lungs. When the gene is switched off, which simulates treatment with Herceptin®, the tumors regress both at the primary sites and in the lung. However, the lung metastases eventually recur, and the tumors are no longer dependent on the initiating event: overexpression of *neu*. This is also the experience with patients who are treated with Herceptin®, who initially respond and have improved survival but whose cancer eventually recurs. This model affords the opportunity to study the mechanism of resistance to Herceptin® and to develop more effective therapies for these very aggressive human tumors.

Widespread genetic change is a hallmark of human cancers, and breast cancer is no exception. The application of analysis tools that permit interrogation of gene expression and genome abnormalities is transforming the rate of discovery of genetic alterations. One such tool is chromosomal comparative genomic hybridization (CGH); using this technique, researchers evaluated a set of human breast tumors and found two loci at which abnormalities of the number of copies of genes correlated with poor survival outcome. They were also able to find a relationship between two other loci and the mutational status of *p53* (Jain et al., 2001). Such analyses contribute to gene discovery and the development of prognostic markers. Deletions and amplifications are frequently observed with CGH; amplicons can be sequenced not only to locate genes, but also to study the mechanisms of amplification and their role in cancer progression. One such amplicon at 20q13.2 was comprehensively analyzed by a variety of techniques and found to contain two genes that appear to drive the development of breast tumors (Collins et al., 2001).

Metastasis and Progression

Complications arising from distant metastases are the eventual cause of death in most breast cancer patients whose tumors have spread from their original locations. At diagnosis, approximately 50% of patients with invasive breast cancer have evidence of axillary lymph node involvement, and the presence of cancer at this site is a powerful prognostic indicator for early recurrence and decreased survival (Fisher et al., 1978; Carter et al., 1989). Depending on the estrogen receptor status of the original tumor, further metastases tend to appear in either the bone and reproductive tract (for ER-positive tumors), or viscera (for ER-negative tumors) (Koenders et al., 1991). Bone metastases occur frequently in breast cancer patients, are quite painful, and are usually fatal. The formation of osteolytic lesions is the result of cooperating events between infiltrating tumor cells and resident osteoclasts in the bone. The release of parathyroid hormone-related protein (PTHrP) from tumor cells stimulates the resorption of bone through direct or indirect activation of osteoclasts. Increased osteolysis leads to the release of the growth factor TGF-β near the tumor site, which in turn stimulates further production of PTHrP by the tumor cells. A vicious cycle is thereby propagated in the skeleton, leading to further bone degradation, hypercalcemia, and, eventually, death. NCI-supported research has demonstrated that the downstream effects of TGF-β are mediated by the intracellular signaling molecules p38 MAPK and Smads (Kakonen et al., 2002), and treatment of breast cancer cell lines with a p38 inhibitor was found to prevent TGF-β-induced PTHrP production. Researchers have also demonstrated that lifetime exposure to a soluble TGF-β antagonist protects mice from metastases in a mouse model of metastatic breast cancer (Yang et al., 2002). These findings have important implications for the treatment and prevention of human breast cancer metastases.

Model systems are beginning to reveal some features of the metastatic cascade and the involvement of signal pathways in promoting metastasis. One recent study investigated the role of TGF-β signaling in the progression of metastatic events from invasion of the primary tumor to the establishment of metastatic foci. The investigators did this by engineering a mouse cancer model that can initiate mammary tumors with *neu* and also express either an activated TGF-β type I receptor or a dominant-negative TGF-β type II receptor (Siegel et al., 2003). The activated type I receptor increased tumor latency and enhanced the formation of the lung metastases, while expression of the type II receptor had the opposite effect. Taken together, the results point to a role for TGF-β in the successful extravasation of the breast cancer cells from pulmonary vessels. Another mammary cancer model was used to study the effect of dietary antioxidants on mammary tumor growth and metastasis. These researchers

found that mice fed an antioxidant-depleted diet had more small primary tumors, fewer large primary tumors, and fewer lung metastases compared with mice fed a diet with normal levels of vitamins A and E. This study may aid in understanding why human intervention trials using antioxidant supplements have produced mixed, and sometimes surprising, results (Albright et al., 2004).

Continuing Needs and Evolution

In their 1998 report, PRG members indicated that more research was needed in the area of normal mammary development, particularly with regard to understanding the principal cell types involved in mammary development and their mechanisms of action. Although the number of projects in NCI's Breast Cancer Research Portfolio addressing mammary gland biology has doubled since the release of the 1998 report, there remains a need for more research in this area. This deficiency could be corrected by increasing the funding for new investigators in this field, facilitating the interface between academic investigators and biotech/pharmaceutical companies, facilitating the collection of human breast tissue samples from a variety of developmental stages, and supporting the development and maintenance of new transgenic or knockout mouse models that mimic normal human mammary development.

Progress in breast cancer research would also be accelerated by the integration of biological information across various model systems. Data gleaned from experiments in cell lines, *ex vivo* models, and *in vivo* models could be incorporated into an integrated cancer biology network that uses dynamic computer-based mathematical models, supported by advanced informatics systems, to model the development of cancer. These models could recapitulate the interactive, dynamic, and spatial relationships between molecules in a cell, between cells, between cells and their microenvironment, and between the organism and the macroenvironment during cancer initiation and progression.

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Chapter 4:
Etiology of Breast Cancer: NCI's Investment and Recent Progress

Research into both the most relevant environmental factors underlying breast cancer and the potential inherited susceptibility factors offers a new opportunity for understanding breast cancer risk. *Charting the Course: Priorities for Breast Cancer Research*

Recent research has identified genetic mutations, lifestyle factors, environmental and occupational exposures, and personal susceptibility factors that appear to be associated with the development of breast cancer. To learn more about the role of genes and gene-environment interactions in the etiology of cancer, NCI is sponsoring the Consortium of Cohorts, which recently began pooling data and biospecimens from ten large cohorts (including the Nurses' Health Study and the Women's Health Study). The Breast and Ovarian Cancer Family Registries collect information and laboratory specimens from 9,000 families with a history of breast and/or ovarian cancer to support research on genetic and environmental susceptibility for these cancers. NCI is also sponsoring the Long Island Breast Cancer Study Project, a multistudy effort to investigate the role of environmental factors in breast cancer in two New York counties.

In its 1998 report, the Breast Cancer PRG identified six priority questions and opportunities that deal with important topics in breast cancer etiology research. These priorities address the need to: identify intermediate markers to help advance our understanding of breast carcinogenesis, ascertain gene-environment interactions, determine which factors influence disease progression, find approaches to expand our knowledge of breast cancer etiology, consider etiologically distinct components of breast cancer, and determine the role of dietary factors in breast carcinogenesis.

The NCI has been responsive to the PRG priorities related to breast cancer etiology. Research has recently assessed the breast cancer risk of women with mutations in the breast and ovarian cancer susceptibility genes BRCA1 and BRCA2 who are not from multiple-case families. Other genetic mutations have been identified that may also increase a woman's susceptibility to breast cancer. In addition, researchers have determined that several environmental toxins and lifestyle factors (including hormone replacement therapy use, exercise, and working at night) appear to be associated with breast cancer risk.

NCI's Investment and Response

From fiscal year 1998 to 2003, NCI's extramural investment in breast cancer etiology research increased from $75.3 million to $107.2 million (Figure 4-1). This increase corresponds to increases in the number of projects that are responsive to the six Breast Cancer PRG research priorities for etiology.

NCI's response to the six Breast Cancer PRG priority research questions for etiology is summarized in Table 4-1.[1]

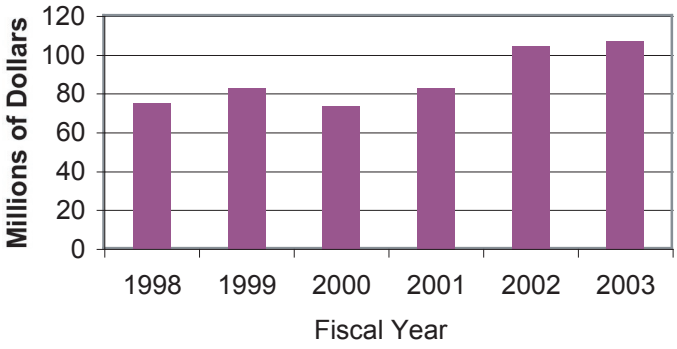


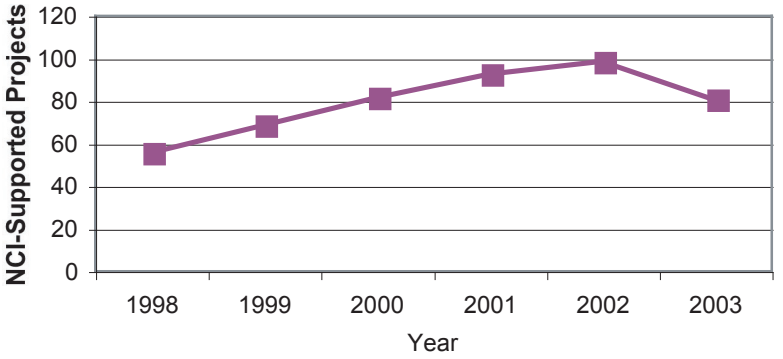
Figure 4-1. NCI's extramural investment in breast cancer etiology research: 1998-2003 (in millions of dollars)

1 A given project may map to more than one PRG priority and therefore be represented in more than one figure. Projects active in 2003 are listed in Appendix B (Tables B-7 to B-13) by Principal Investigator's name for each PRG priority.

Table 4-1. NCI Efforts Responsive to PRG Priorities and Opportunities in Etiology[a]

PRG Priority:

What types of intermediate markers would be useful to advance our understanding of mechanisms involved in breast carcinogenesis?

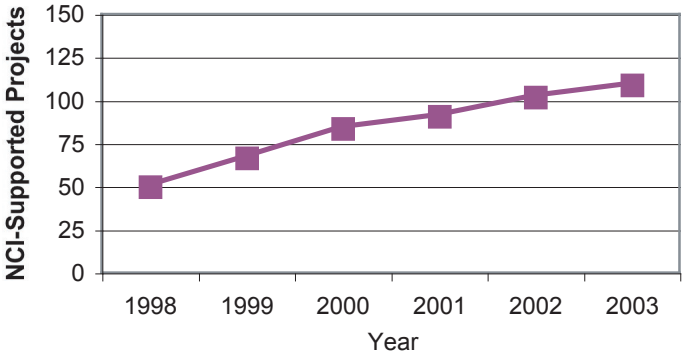


NCI Efforts:

- In FY003, examples of active areas of investigation included genes as potential markers of accelerated cellular senescence, secreted proteins as breast cancer prevention markers, the signaling pathways by which heregulin regulates the expression and activation of the urokinase plasminogen activator (uPA)/uPA receptor system, and the relationships between breast cancer incidence and plasma levels of premenopausal hormones.
- NCI initiatives addressing this priority included the Cancer Genome Anatomy Project (CGAP), Cancer Molecular Analysis Project (CMAP), Cancer Research Small Grant Program, Cooperative Human Tissue Network (CHTN), and Director's Challenge: Toward a Molecular Classification of Cancer.

PRG Priority:

What are the best approaches to understanding gene-environment interactions?[b]



NCI Efforts:

- In fiscal year 2003, examples of active areas of investigation included inter-individual variations in cancer risk defined by allele variant genes and environmental and endogenous risk factors; models of cancer that take into account genetic predisposition (BRCA 1/2 status), reproductive history, and exposure to hormones; the interaction between tobacco smoke and NAT2 or COMT genetic polymorphisms; genetic polymorphisms in the genes related to tamoxifen and estrogen bioavailability; and the effect of the timing of dietary factors on mammary tumorigenesis and the mechanisms mediating these associations.
- Examples of clinical trials addressing these priorities included the following:
  - Comparative Genetic Study of Susceptibility Genotypes and Protein Expression in Healthy Women, Women at High Risk for Breast Cancer, and Women With Breast Cancer (NCI-00-C-0079)
  - Study of Clinical, Genetic, Behavioral, Laboratory, and Epidemiologic Characteristics of Individuals and Families at High Risk of Breast or Ovarian Cancer (NCI-02-C-0212)

a. Some of the original PRG priorities are addressed jointly in Table 4-1 because these priorities address partially overlapping issues and they are relevant to many of the same research projects and initiatives.

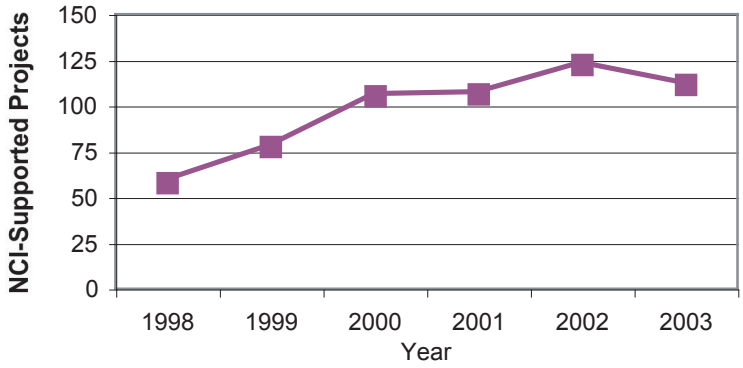
b. This priority merges the two original PRG priorities: "What are the best approaches to understanding gene-environment interactions?" from the Etiology section and "Do any life experiences, behaviors, or environmental exposures influence breast cancer risk among women with inherited mutations in major predisposing genes?" from the Genetics section in the original Breast Cancer PRG report.

- NCI initiatives addressing this priority included Breast and Ovarian Cancer Family Registries (CFRs) and Cancer Genetics Network (CGN).

PRG Priority:

What factors influence disease progression?

NCI Efforts:

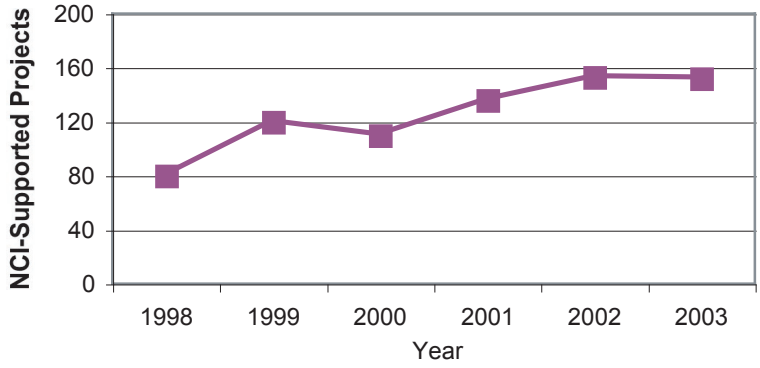


- In FY2003, examples of active areas of investigation included the association between recurrence of breast carcinoma *in situ* and modifiable lifestyle factors, post-treatment behavioral risk factors for recurrence of secondary breast tumors or new primaries, regulation of breast cancer growth by activation peptide, and the role of EGF-related peptides in the pathogenesis of breast and colon cancer.
- NCI initiatives addressing this priority included the Breast Cancer Faculty, the Cancer Genome Anatomy Project, and Small Grants Program for Cancer Epidemiology.

PRG Priority:

What might be a useful approach to expanding our knowledge regarding breast cancer etiology?

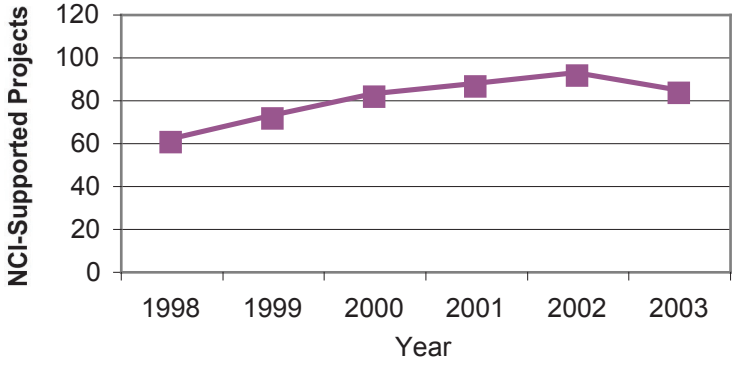
NCI Efforts:



- In FY2003, examples of active areas of investigation included reasons for ethnic variations in cancer incidence; population-based case-control studies to investigate the relationship between postmenopausal hormone therapy and breast cancer mortality and between lifestyle factors and breast cancer incidence; a training program in cancer epidemiology, biostatistics, and environmental health sciences; the use of telomerase in new model systems of human cancer; and understanding puberty and environmental factors that may influence puberty, the timing of which is an important risk factor for breast cancer.
- On November 1-5, 2003, NCI co-sponsored the *24th Congress of the International Association for Breast Cancer Research—Advances in Human Breast Cancer Research: Preclinical Models*, as well as a workshop on *Genomic and Proteomic Technological Advances in Cancer Research*.
- NCI initiatives addressing this priority included the Breast and Ovarian Cancer Family Registries, Cancer Genetics Network, Cancer Molecular Analysis Project, Cooperative Human Tissue Network, and NCI Cohort Consortium.

PRG Priority:

Are there etiologically distinct components of breast cancer that it would be useful to consider?

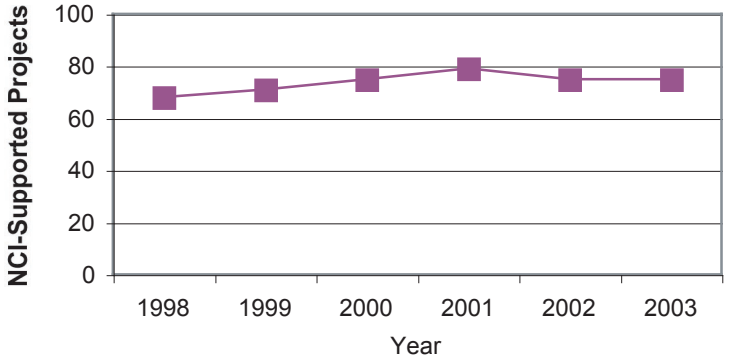


NCI Efforts:

- In FY2003, examples of active areas of investigation included the function of Her4 as a potential differentiation factor in human breast cancer, pregnancy hormone levels affecting breast differentiation and proliferation in women with different levels of breast cancer risk, and the metabolic factors of obesity/weight changes and indicators of insulin status as they relate to breast and endometrial cancers.
- On November 1-5, 2003, NCI cosponsored the *24th Congress of the International Association for Breast Cancer Research—Advances in Human Breast Cancer Research: Preclinical Models*, as well as a workshop on *Genomic and Proteomic Technological Advances in Cancer Research*.
- NCI initiatives addressing this priority included the Breast SPOREs, Cancer Molecular Analysis Project, Director's Challenge: Toward a Molecular Classification of Tumors, and NCI Cohort Consortium.

PRG Priority:

What types of studies should be pursued to advance our understanding of the role of dietary factors in breast carcinogenesis?



NCI Efforts:

- In FY2003, examples of active areas of investigation included the relationship between energy balance and cancer risk in African-American women, the association between dietary intake of isothiocyanates and d-limonene and risk of breast cancer recurrence, the effects of dietary fat and peroxisome proliferator-activated receptor gamma on breast cancer progression, and the ability of high-selenium garlic to suppress the clonal expansion of mammary preneoplastic lesions.
- Examples of clinical trials addressing this priority included the following:
  - Dietary Intervention in Women at High Risk for Breast Cancer (WSU-H-018296)
  - Randomized Dietary Intervention Study of a Diet Rich in Vegetables, Fruit, and Fiber and Low in Fat in Women With Previously Treated Stage I, II, or III Breast Cancer (UCSD-980919)
  - Phase II Trial of Dietary Fatty Acids: Roles in Hormonally Mediated Cancers in Normal Premenopausal Women (UMN-9509M10234)
- On October 14-16, 1998, NCI sponsored the 5 A Day International Symposium, whose goals included reviewing the scientific link between increased consumption of fruits and vegetables and the reduced risk of disease.
- NCI initiatives addressing this priority included the Cancer Research Small Grant Program and NCI Cohort Consortium.

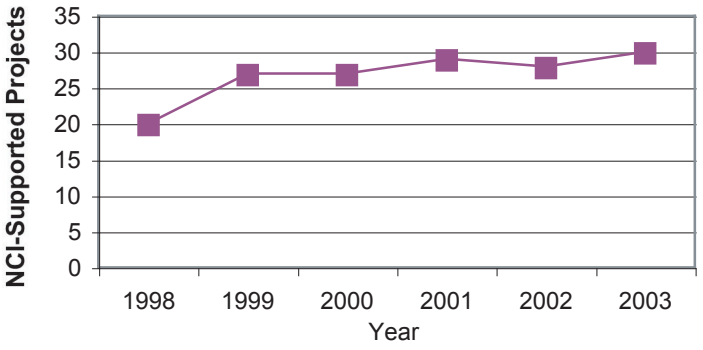
Additional Breast Cancer Etiology Projects

NCI Efforts:

- Although cancer health disparities were not addressed by this PRG in its report, several areas of investigation on this topic were active in FY2003, including the role of diet on breast cancer in Puerto Rican women; the association of breast cancer in black and white women with body size, diabetes, and dietary patterns; nutritional and metabolic

determinants of cancer in Asian women; and differences between gene and antigen expression profiles and mutational events in black and white women.

- In FY2003, other examples of active areas of investigation included the role of BRCA1 in maintaining genome integrity; the complex stromal/epithelial interactions involved in the initiation and development of breast cancer; and the functional analysis of breast cancer susceptibility genes in mice.



The initiatives relevant to research on breast cancer etiology between FY1998 and 2003 include the following list of general initiatives that are described in Table 2-1[2] (Chapter 2) and the category-specific initiatives that are listed and described in Table 4-2.[3]

- Aging Women and Breast Cancer
- Breast and Ovarian Cancer Family Registries (CFRs)
- Breast Cancer Faculty
- Cancer Biomedical Informatics Grid (caBIG)
- Cancer Centers Program
- Cancer Genetics Services Directory
- Cancer Genome Anatomy Project (CGAP)
- Cancer Research Small Grant Program
- Cancer Research Training, Career Development, and Education Opportunities
- Clinical Trials Cooperative Group Program
- Competing Supplements for Organotypic Models of Cancer
- Cooperative Breast Cancer Tissue Resource (CBCTR)
- Cooperative Human Tissue Network (CHTN)
- Correlative Studies Using Specimens from Multi-Institutional Treatment Trials
- Director's Challenge: Toward a Molecular Classification of Tumors
- Exploratory Grants for Correlative Laboratory Studies and Clinical Trials
- Improving DNA, RNA, and Protein Availability in Fixed Tissue
- Insight Awards to Stamp Out Breast Cancer
- Minority Institution/Cancer Center Partnership (MI/CCP)
- Molecular Target Drug Discovery for Cancer

[2] Initiatives that impact multiple categories of breast cancer research.

[3] Initiatives that are unique to this chapter on etiology.

- Mouse Models of Human Cancers Consortium
- NCI Center for Bioinformatics (NCICB)
- Shared Pathology Informatics Network (SPIN)
- Shared Resources for Scientists Outside NCI Cancer Centers
- Small Animal Imaging Resource Program (SAIRP)
- Small Grants Program for Cancer Epidemiology
- Southern Community Cohort Study (SCCS)
- Specialized Programs of Research Excellence (SPOREs) in Breast Cancer
- Specimen Resource Locator

Table 4-2. NCI Initiatives Relevant to Breast Cancer Research: Etiology

Initiatives Focused on Breast Cancer Research

- Long Island Breast Cancer Study Project (http://epi.grants.cancer.gov/LIBCSP/Overview.html)
  - Overview: A multistudy effort to investigate whether environmental factors are responsible for breast cancer in Suffolk, Nassau, and Schoharie Counties, New York, and in Tolland County, Connecticut.
  - Relevant Resource Resulting From This Initiative: Findings from the Breast Cancer and the Environment on Long Island Study, reported in 2002, found no association between breast cancer and either organochlorine compounds such as the pesticide DDT or electromagnetic fields. The study also revealed a small increased risk of developing breast cancer in women exposed to polycyclic aromatic hydrocarbons. In this study population, an analysis of aspirin and breast cancer risk found that use of this medication was linked to hormone-receptor-positive breast cancer but not to hormone-negative breast cancer (Terry et al., 2004). In addition, the NCI developed a health-related Geographical Information System (LI-GIS), which provides researchers with an advanced tool to investigate relationships between breast cancer and the environment and to estimate exposures to environmental contamination in Long Island.
- Breast Cancer and the Environment Research Centers (RFA-ES-03-001)
  - Overview: This National Institute of Environmental Health Sciences (NIEHS) and NCI jointly supported initiative supports four research centers that will work collaboratively on several fronts. Using animals, they will study the development of mammary tissue and the effects of specific environmental agents. In the second collaborative project, they will enroll different ethnic groups of young girls and study their life exposures to a wide variety of environmental, nutritional, and social factors that impact puberty. Early puberty has been shown to increase breast cancer risk later in life. All the centers will work with advocacy groups to add their insight and experience to the research effort.
  - Relevant Projects Resulting From This Initiative:

    Puberty and Cancer Initiation: Environment Diet and Obesity

    Bay Area Breast Cancer and the Environment Research Center

    Breast Cancer and the Environment Research Center

    Center for Environment and Mammary Gland Development

- Regional Variation in Breast Cancer Rates in the U.S. (RFA-CA-98-017)
  - Overview: Supports interdisciplinary epidemiologic studies to better understand determinants of regional variations in breast cancer incidence and mortality rates in the United States.
  - Relevant Research Projects Resulting From This Initiative: Between 1998 and 2003, five projects relevant to breast cancer research were supported through this Request for Applications (RFA).

Initiatives With Breast Cancer-Relevant Components

- Cancer Genetics Network (CGN) (http://epi.grants.cancer.gov/CGN)
  - Overview: A national network of centers specializing in the study of inherited predisposition to cancer.
  - Relevant Research Projects Resulting From This Initiative: The CGN database contains information from 15,760 families that have a history of cancer. Data on each enrollee include demographic information, medical history, and four-generation family cancer history. Three recent pilot studies addressed issues relevant to breast cancer:

    High-Risk Breast Cancer Screening Pilot Study

    Validation of BRCA1 and 2 Carrier Probability Models

    Genetic and Environmental Modifiers of Penetrance in BRCA1 and BRCA2 Mutation Carriers
- Cohort Studies in Cancer Epidemiology (PAS-02-009)
  - Overview: Coordinates the submission, review, and funding of epidemiologic cohort studies. Cohort studies are well suited for the evaluation of gene-gene and gene-environment interactions in a prospective manner.
  - Relevant Research Projects Resulting From This Program Announcement (PA): Between 1998 and 2003, four projects relevant to breast cancer research were supported through this PA. Specific projects can be found in Appendix B, Tables B8, B10, and B12, by searching for the PA number.
- Diet, Lifestyle, and Cancer in U.S. Special Populations (PA-98-028)
  - Overview: Supports studies to elucidate causes of cancer and means of prevention in African Americans, American Indians, Alaska Natives, Asian and Pacific Islanders, Native Hawaiians, Hispanics, and rural, older, low-income, and low-literacy groups. These groups experience unusually high cancer incidence and mortality for some cancer sites though the environmental and genetic reasons are not well understood.
  - Relevant Research Projects Resulting From This PA: Between 1998 and 2003, three projects relevant to breast cancer research were supported through this PA. Specific projects can be found in Appendix B, Tables B8, B10, and B11, by searching for the PA number.
- Geographic-Based Research in Cancer Control and Epidemiology (PAS-00-120)
  - Overview: Supports the use of the *Atlas of Cancer Mortality in the United States, 1950-1994* to identify the reasons for the geographic variation in specific cancers, including the clustering of areas with high or low incidence and/or mortality rates.
  - Relevant Research Projects Resulting From This PA: Between 1998 and 2003, one project relevant to breast cancer research was supported through this PA:

    A Geographic Information System-Based Workbench to Interpret Cancer Maps

- Interdisciplinary Studies in the Genetic Epidemiology of Cancer (RFA-CA-98-018)
  - Overview: Supports collaborative and interdisciplinary genetic epidemiology investigations designed to identify and evaluate the interactions of genetic and epidemiologic risk factors leading to cancer susceptibility in individuals, families, and populations and factors influencing the rate of increase with age in cancer susceptibility.
  - Relevant Research Projects Resulting From This RFA: Between 1998 and 2003, one project relevant to breast cancer research was supported through this RFA:

    Breast Cancer, Radiation Exposure, and the ATM Gene
- NCI Cohort Consortium (http://cancercontrol.cancer.gov/bb/cohort_conso.html)
  - Overview: Large consortium of investigators pooling information on study participants from multiple studies in an effort to understand the interaction between cancer-predisposing genes and environmental factors such as chemicals, diet, and pharmacological agents.
  - Relevant Resources Resulting From This Initiative: High-quality exposure and cancer data from 700,000 individuals and their biological specimens will be used for genetic analysis studies. A first "proof of principle" study will focus on breast and prostate cancer and seek to identify important gene-environment interactions in hormonal synthesis and metabolic pathways.

Ongoing NCI Research: Recent Progress in Breast Cancer Etiology

BRCA1 and BRCA2

Mutations in the breast and ovarian cancer susceptibility genes BRCA1 and BRCA2 are observed in a large proportion of families in which several members have had breast cancer. As commercial testing for BRCA1 mutations has become accepted, more BRCA1 mutation carriers are being identified in cancer risk evaluation programs. Some women in these programs who learn that they have these mutations choose to undergo prophylactic mastectomy and/or oophorectomy because of their extremely high cancer risk—78% according to one cancer risk evaluation program, in comparison to a lifetime risk estimate of 13% for all women (Brose et al., 2002; Ries et al., 2004). Research has recently addressed the breast cancer risk of women with mutations in BRCA1 or BRCA2 who are not from multiple-case families.

One study found that Ashkenazi Jewish women who inherited mutations in the BRCA1 and BRCA2 genes had an 82% lifetime risk of breast cancer—similar to that of women in families with many breast cancer cases (King et al., 2003). Another study showed that women who carry BRCA1 mutations have a higher average risk of breast cancer (65%) than BRCA2 carriers (45%), but this difference decreases after age 50 (Antoniou et al., 2003). For women with BRCA1 mutations, those identified who are referred to or seek counseling at cancer risk evaluation clinics have a higher risk of breast cancer (73%) than women in population-based studies (35%-50%) and a lower risk than women from multiple-case families (Brose et al., 2002).

Research is also addressing behavioral modifiers of breast cancer risk among BRCA1 and BRCA2 carriers. One study found that taking oral contraceptives was not associated with an increased risk of breast cancer among BRCA2 mutation carriers. But BRCA1 mutation carriers who had ever used oral contraceptives—especially if they had used them for more than 5 years or before age 30—had an increased risk of developing early-onset breast cancer (Narod et al., 2002). Although previous research indicated that smoking increased the risk of developing hereditary breast cancer, a recent study found no significant impact on breast cancer risk in BRCA1 or BRCA2 carriers who were current or previous smokers (Ghadirian et al., 2004).

Other Breast Cancer Susceptibility Genes

BRCA1 and BRCA2 gene mutations can increase breast cancer risk substantially, but these mutations are rare and explain only a small proportion of the clustering of breast cancer in certain families. According to recent research, only 5%-10% of breast cancers diagnosed in women younger than 40 years can be attributed to mutations in these genes (Dite et al., 2003). Researchers are therefore studying other candidate susceptibility genes.

One possibility is CHEK2, a gene that encodes a cell-cycle checkpoint kinase that is implicated in DNA repair processes involving BRCA1 and *p53*. Researchers have found that a variant of CHEK2, CHEK2(*)1100delC, is found in 1.1% of healthy individuals, 5.1% of individuals with breast cancer from families that do not carry mutations in BRCA1 or BRCA2, and 13% of individuals from families with male breast cancer. The investigators estimate that this variant increases breast cancer risk about twofold in women and tenfold in men, although it does not increase risk in carriers of BRCA1 or BRCA2 mutations (Meijers-Heijboer et al., 2002).

Another potential susceptibility gene is the ATM gene, which is mutated in ataxia-telangiectasia. One analysis found two ATM mutations (IVS10–6T®G and T7271G) in 4% of families with multiple breast cancer cases that did not carry the BRCA1 or BRCA2 mutations. The risk associated with these mutations was strong enough for them to cause multiple cases in families (Chenevix-Trench et al., 2002). Another study found several variants of ATM in families with a history of breast cancer, ovarian cancer, or both, but not in families with no history of breast cancer (Thorstenson et al., 2003).

Other genes that may play a role in influencing breast cancer risk independently or together with other environmental, behavioral, or endogenous factors include those involved in estrogen synthesis, such as CYP19 (Han et al., 2004), and DNA repair, such as members of the XRCC gene family (Haiman et al., 2003).

Environmental Influences

Several environmental pollutants have been hypothesized to be involved in the development of breast cancer. The Long Island Breast Cancer Study Project is a federally mandated, population-based case-control study sponsored in part by NCI to determine whether breast cancer risk among women in Nassau and Suffolk Counties, New York, is associated with certain environmental exposures.

The Long Island investigators found little evidence of an increased risk of breast cancer from exposure to organochlorines, including the pesticide DDT and the industrial chemical PCBs, based on assessments of the levels of these chemicals in blood (Gammon et al., 2002b). In addition, analysis of extensive electromagnetic field exposure measurements in this population yielded evidence that electromagnetic field exposure was not a risk factor for breast cancer (Schoenfeld et al., 2003). The Long Island Study researchers also investigated the association between polycyclic aromatic hydrocarbon (PAH) compounds—some of which have been categorized by the Environmental Protection Agency as probable or possible human carcinogens—and breast cancer risk. Major sources of human exposure to PAH compounds include combustion products of fossil fuels and cigarette smoking, as well as grilled and smoked foods. The investigators found that women with high PAH-DNA adduct levels had a 50% higher risk of breast cancer than women with lower adduct levels, although they observed no dose-response effect (Gammon et al., 2002a).

Behavioral Factors

Millions of women in the United States have taken hormone replacement therapy (HRT) to relieve menopausal symptoms and prevent chronic diseases, including heart disease and osteoporosis. But recent research has shown that the benefits of HRT are limited to management of menopausal symptoms and the prevention of osteoporosis and colorectal cancer. However, results of the Women's Health Initiative trial of combined estrogen and progestin showed that overall health risks exceed these benefits. The study showed that relatively short-term use of combined estrogen and progestin increases the risk of cardiovascular disease, blood clots, and breast cancer and that these cancers are more likely to be diagnosed at more advanced stages in women using the therapy than in women not using the therapy (Chlebowski et al., 2003). Another study showed that women who take combined estrogen and progestin regimens increase their risk of breast cancer each year by about twice as much as women who take estrogen alone (Newcomb et al., 2002).

Obesity is a known risk factor for breast cancer. Recent research has shown that heavier postmenopausal women (body mass index [BMI] >31), especially postmenopausal women under the age of 65, have more than twice the breast cancer risk of slimmer women (BMI <23). Changes in BMI and weight since age 18 were also found to be associated with breast cancer. Some studies suggest that obesity is a risk factor only among women who have never taken HRT (Morimoto et al., 2002). Other investigators have shown that women can reduce their breast cancer risk through exercise. Sustained activity throughout life, and especially activity after menopause, can reduce the risk of breast cancer substantially (Friedenreich et al., 2001).

Endogenous Factors

Some potentially important new predictors of risk have been identified through the prospective Nurses' Health Study. Researchers have identified a positive relationship between levels of circulating insulin-like growth factor and breast cancer risk in premenopausal women (Hankinson et al., 1998). An association has also been found between plasma prolactin, a hormone that is essential for mammary gland development and lactation, and breast cancer risk. Women with high levels of prolactin have about twice the breast cancer risk of women with low levels of the hormone (Hankinson et al., 1999). Levels of another hormone, melatonin, may have an impact on breast cancer risk. Melatonin serum levels decrease when people are exposed to light at night. When researchers tested nurses who work night shifts, they found that women who worked on rotating night shifts had a greater risk of breast cancer than those who never worked these shifts; these risks were highest in women who had worked night shifts for 30 or more years (Schernhammer et al., 2001).

Continuing Needs and Evolution

A promising direction of genetics research is to develop prevention, screening, and prognostic applications; however, progress in understanding how genes and specific genotype patterns affect risk for breast cancer has been limited by the design and size of genetic studies. For some of the genes that appear to be associated with the risk of breast cancer development or progression, the small scale of the studies has led to contradictory results among different research groups. Large-scale, multi-institutional studies are now being conducted to validate the association and causation of putative susceptibility genes with breast cancer risk, incorporating advanced genomic analyses by haplotyping and genomic scans to address the complexities of genetic and environmental interrelationships. Genetic etiology studies are collecting and analyzing data on other lifestyle and environmental factors to identify linkages between certain genes and the environment. The development of nationwide and international cohorts requires a standardized mechanism for collecting, analyzing, and reporting data and enhanced resources to support these studies.

There is a continuing need to improve the estimates of the magnitude of risk associated with BRCA1 and certain other mutations. While these genes are clearly important, there are a number of different mutations involved, and the risk estimates for developing breast cancer vary widely—in part because of differences in study designs. Women who consider being tested for mutations in these genes need to make decisions based on the best possible estimates of risk, as being tested has profound implications for both the women who are tested and their family members in terms of quality of life and medical decisions regarding the potential use of preventive measures (e.g., chemoprevention or surgical procedures).

A better understanding is needed of the role of endogenous hormones—especially hormones that have not been well studied with respect to breast cancer, such as prolactin and progesterone. It is also important to understand exogenous and lifestyle factors that contribute to endogenous hormone levels. Techniques are needed to better measure hormones, understand their interrelationships, and clarify how peripheral measurement of hormones is related to local production in breast tissue. Such information may be useful in further developing chemopreventive approaches given evidence showing that tamoxifen has protective effects against the development of breast cancer.

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Thorstenson YR, Roxas A, Kroiss R, Jenkins MA, Yu KM, Bachrich T, Muhr D, Wayne TL, Chu G, Davis RW, Wagner TM, Oefner PJ. Contributions of ATM mutations to familial breast and ovarian cancer. Cancer Res. 2003 Jun 15;63(12):3325-3333.

Chapter 5:
Breast Cancer Prevention: NCI's Investment and Recent Progress

The goal of breast cancer prevention research is to develop readily acceptable, minimally toxic, and affordable strategies that will reduce breast cancer incidence, morbidity, and mortality without inducing increased morbidity and mortality from other conditions. *Charting the Course: Priorities for Breast Cancer Research*

Recent advances in fields of biology, genetics, and epidemiology have led to an increased understanding of the risk factors that predispose certain individuals to cancer. It has become clear in recent years that certain genetic, hormonal, dietary, and other lifestyle influences play an important role in the development of breast malignancies. These influences may be mediated indirectly by several factors, such as early full-term pregnancy or exercise. The NCI continues to address the challenges of identifying the relevant risk factors and enabling the development of effective preventive agents and strategies that delay or inhibit the clinical onset of invasive disease. Prevention research is also aimed at reducing the incidence of secondary breast tumors that may arise in the months or years following treatment for the initial breast cancer.

In 1998, the Breast Cancer PRG identified seven priorities that deal with important topics in breast cancer prevention research. These priorities address the need to create models of precancerous biology, identify surrogate endpoint biomarkers of breast cancer development, determine the essential changes in breast cancer initiation, determine the efficacy of preclinical prevention trials, increase the number of Phase II trials that test novel preventive agents and strategies, increase the efficiency of accrual to Phase III clinical trials, and effectively use human models to determine the optimal dosage of chemopreventive agents.

The NCI has been responsive to PRG priorities related to breast cancer prevention. Genetic mutations comparable to their human disease counterparts have been used to construct mouse models that develop precancerous lesions as well as breast cancer. These models provide a wealth of information about factors involved in breast cancer initiation and have been used to determine the effectiveness of a variety of agents and strategies for the prevention of breast cancer. A large-scale NCI-sponsored clinical trial led to FDA approval of tamoxifen as a chemopreventive agent in high-risk women, and NCI-sponsored researchers are pursuing trials that will assess the effectiveness of other chemotherapeutic regimens in reducing breast cancer incidence.

NCI's Investment and Response

From FY1998 to 2003, NCI's extramural investment in breast cancer prevention research increased from $28.9 million to $43.7 million (Figure 5-1). This increase in funding corresponds to increases in the number of projects that are responsive to the seven Breast Cancer PRG research priorities for prevention.

NCI's responsiveness to breast cancer prevention research is summarized in Table 5-1 for the seven original PRG prevention priorities and two of the original PRG genetics priorities.[1]

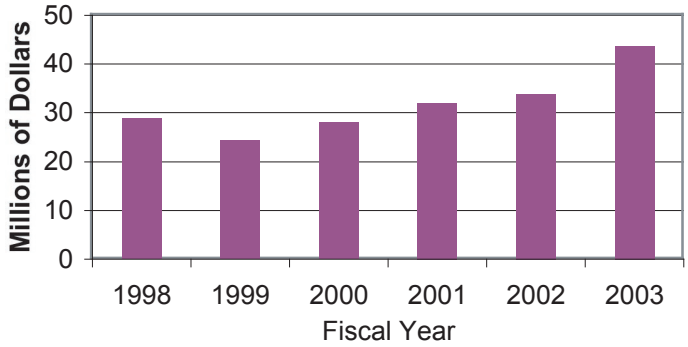


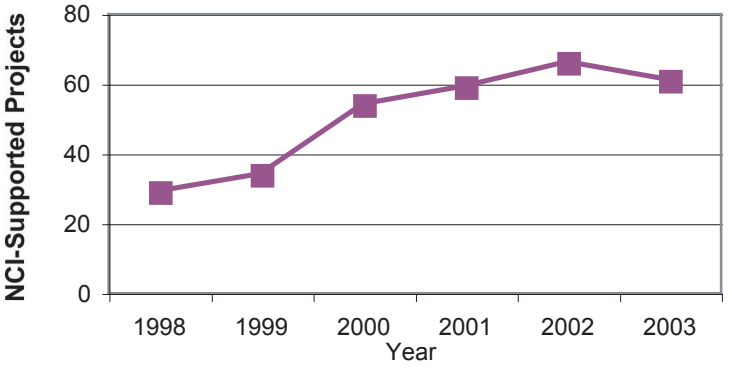
Figure 5-1. NCI's extramural investment in breast cancer prevention research: 1998-2003 (in millions of dollars)

1 A project may map to more than one PRG priority and therefore be represented in more than one figure. Projects active in 2003 are listed by Principal Investigator's name for each PRG priority in Appendix B (Tables B-14 to B-23).

Table 5-1. NCI Efforts Responsive to PRG Priorities and Opportunities in Prevention

PRG Priority:

Better models of precancerous biology are urgently needed. These include animal and xenograft models, human precancerous cell lines, and *in vivo* human precancerous models for long-term study.

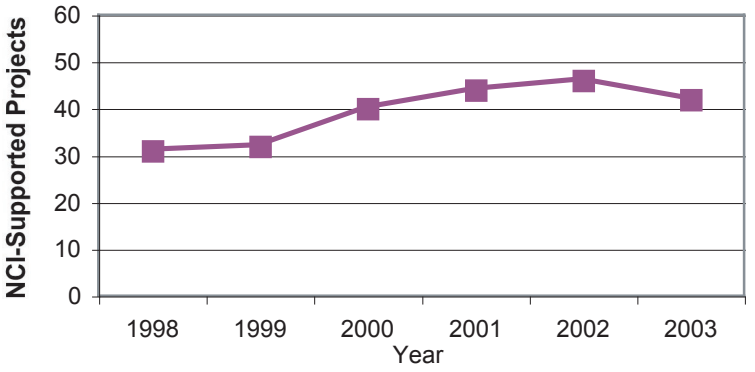


NCI Efforts:

- In FY2003, examples of active areas of investigation included growth of human tumor cell lines in protein-free/hormone-free media, mammary tumorigenesis in inbred and feral mice, breast cancer development in female mice from a transgenic model of prostate cancer, functional analysis of breast cancer susceptibility genes in mice, prevention of mammary cancer in Her2/*neu* transgenic mice, new models of human cancer, screening various chemopreventive agents, MNU-induced rat mammary tumors, and human cell-based systems for screening chemopreventive agents *in vitro*.
- Examples of evolving preclinical chemopreventive agent screening systems include normal human mammary epithelial cells that spontaneously escape senescence and acquire genomic changes (Romanov et al., 2001) and prevention of breast epithelial cell immortalization with chemopreventive and antitelomerase agents (Herbert et al., 2001).
- On September 5-6, 2002, NCI sponsored the *Nutritional Genomics and Proteomics in Cancer Prevention* meeting, which included workshops on model systems.
- NCI initiatives addressing this priority included Competing Supplements for Organotypic Models of Cancer and the Mouse Models of Human Cancer Consortium.

PRG Priority:

Delineate the key surrogate endpoint biomarkers (SEBs) for breast cancer development.



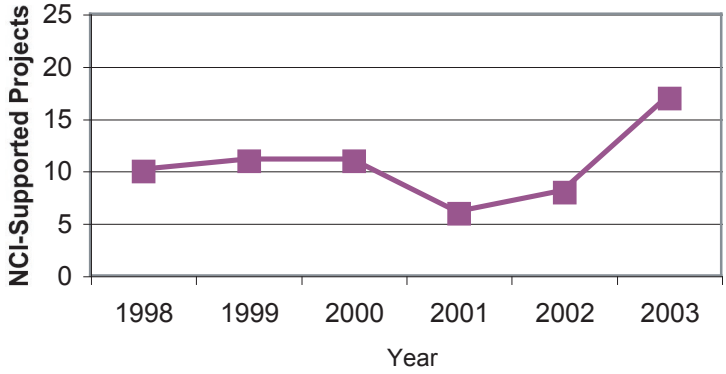
NCI Efforts:

- In FY2003, examples of active areas of investigation included biological markers of breast cancer and tamoxifen response, biomarker modulation by COX-2 inhibitors, detection of breast cancer protein signatures in body fluid, characterization of a novel breast-specific mucin gene, molecular characterization of breast basal-like tumors, *p53* in benign breast disease and breast cancer risk, preclinical evaluations of candidate intermediate endpoints and their modulation by chemopreventive agents, and the molecular profile of inflammatory breast cancer.
- Examples of clinical trials addressing this priority included the following:
  - Phase II Chemoprevention Study of Celecoxib in Premenopausal Women at High Risk for Estrogen Receptor-Negative Breast Cancer (KUMC-HSC-8919-02)
  - Randomized Chemoprevention Study of Bexarotene in Women at High Genetic Risk for Breast Cancer (BCM-H-9315)

- NCI initiatives addressing this priority included the Cancer Genome Anatomy Project (CGAP), Cancer Prevention Research Small Grants Program, and Cooperative Human Tissue Network (CHTN).

PRG Priority:

Determine the degree to which preclinical prevention trials are indicative of outcomes in humans.

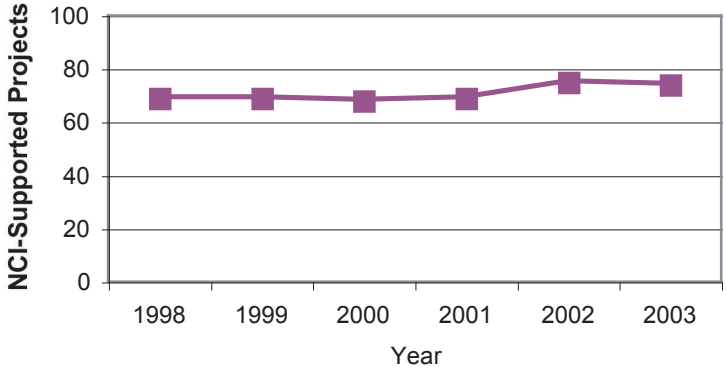


NCI Efforts:

- In FY2003, examples of active areas of investigation included the use of human prolactin antagonist as a chemopreventive agent, combination chemoprevention of estrogen receptor (ER)-negative breast cancer, synthetic peptides from alpha-fetoprotein that prevent breast cancer, multiantigen vaccines for breast cancer prevention, molecular biomarkers of selenium chemoprevention, prevention of breast cancer using selective retinoids, and modulation of carcinogenesis by monoterpenoids.
- NCI initiatives addressing this priority included Chemoprevention in Genetically-Identified High-Risk Groups and Chemoprevention of Estrogen Receptor (ER)-Negative Breast Cancer: Preclinical Studies.

PRG Priority:

Increase the number of new agents and strategies evaluated by increasing the number of Phase II pivotal trials, with biomarker modulation as the measure of efficacy.



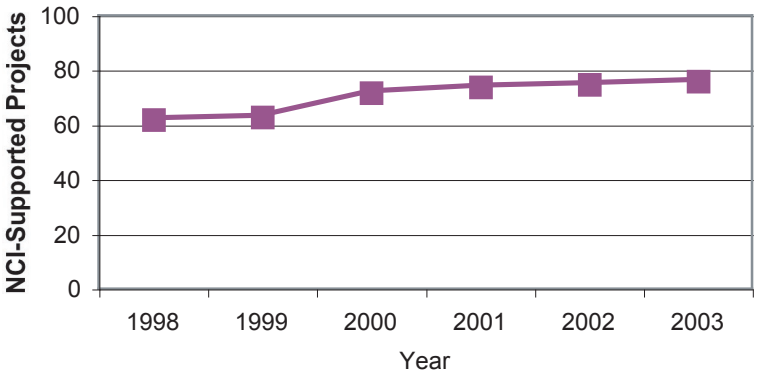
NCI Efforts:

- In FY2003, examples of active areas of investigation included a trial to assess the impact of a low-fat diet on breast cancer recurrence, a chemoprevention pilot trial examining the influence of tamoxifen on candidate surrogate endpoint biomarkers, the effect of phytochemicals on estrogen-enhanced cancers, the role of antioxidants in breast cancer prevention, and EGFR pathway modulation in ductal carcinoma *in situ*.
- Examples of clinical trials addressing this priority included the following:
  - Phase II Randomized Study of Polyphenon E (Green Tea Extract) and Low-Dose Aspirin in Women at High Risk for Developing Breast Cancer (UCLA-0305011)
  - An Exploratory Study to Identify Potential Surrogate Endpoint Biomarkers That Are Modulated by Tamoxifen vs. Placebo in Women with an Increased Risk for Breast Cancer (UTSWMC #0799-302, N01-CN-95139)
  - Phase II Chemoprevention Study of Celecoxib in Premenopausal Women at High Risk for Estrogen Receptor-Negative Breast Cancer (KUMC-HSC-8919-02)
- On October 22, 2001, NCI sponsored the workshop Clinical Trial Design for the Molecular Targets Faculty. On July 28-August 3, 2001, NCI sponsored the American Society of Clinical Oncology (ASCO)–American Association for Cancer Research (AACR) *Educational Workshop: Methods in Clinical Cancer Research*.

- NCI initiatives addressing this priority included Chemoprevention in Genetically Identified High-Risk Groups, Community Clinical Oncology Program (CCOP), and the Rapid Access to Preventive Intervention Development (RAPID) Program.

PRG Priority:

Increase Phase III accrual efficiency and maximize scientific information gleaned (e.g., validation of SEB and conduct of behavioral and outcomes research).

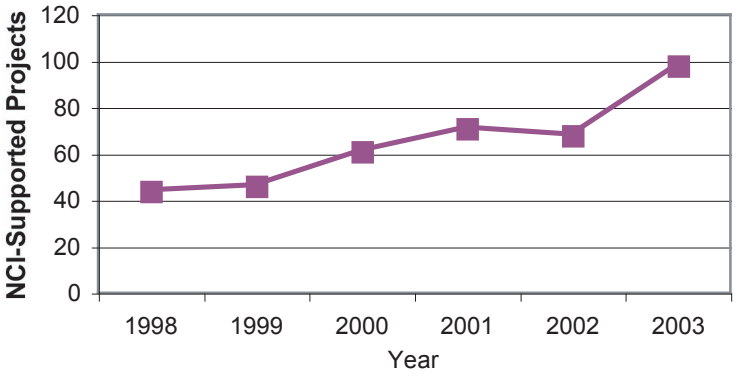


NCI Efforts:

- In FY2003, examples of active areas of investigation included an exercise intervention study to combat fatigue in cancer patients and numerous clinical trials conducted at community clinical oncology program sites.
- Examples of clinical trials addressing this priority included the following:
  - Phase III Randomized Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer (NASBP-P-2)
- NCI initiatives addressing this priority included the Clinical Trials Cooperative Group Program, Community Clinical Oncology Program (CCOP), and Minority-Based CCOPs.

PRG Priority:

What are the essential changes in breast cancer initiation?

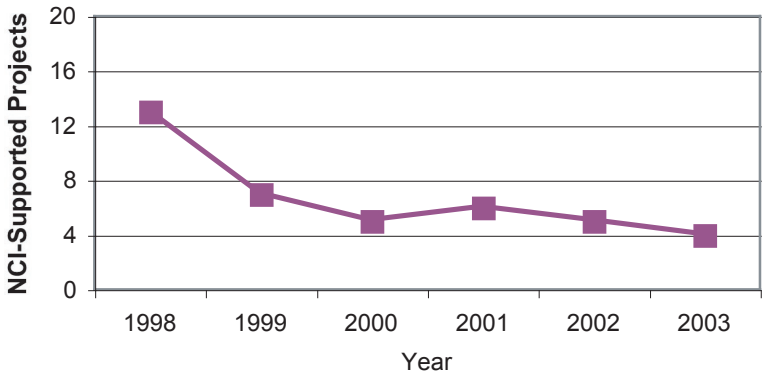


NCI Efforts:

- In FY2003, examples of active areas of investigation included the biology of vascular epithelial growth factors in the mammary gland, signal transduction pathways of TGF-β, the role of CCAAT/enhancer-binding protein transcription factors in regulating cell growth and tumorigenesis, *p53* in benign breast disease and breast cancer risk, p27KIPL deficiency as a potential promoter of carcinogenesis, the role of fibroblasts and IGF-II in breast carcinogenesis, nucleoside transporters as chemoprevention targets, and X-linked genes in breast and ovarian cancer etiology.
- Examples of clinical trials addressing this priority included the following:
  - Phase II Chemoprevention Study of Celecoxib in Premenopausal Women at High Risk for Estrogen Receptor-Negative Breast Cancer (KUMC-HSC-8919-02)
  - Phase II Randomized Chemoprevention Study of LY353381 Hydrochloride in Women With Fine Needle Aspiration Cytologic Evidence of Hyperplasia and at High Risk for Breast Cancer (KUMC-HSC-7264-97)
- NCI initiatives addressing this priority included the Cancer Molecular Analysis Project (CMAP) and Cooperative Breast Cancer Tissue Resource (CBCTR).

PRG Priority:

Are we using appropriate human models in Phase I and II testing for optimal chemoprevention dose range finding?

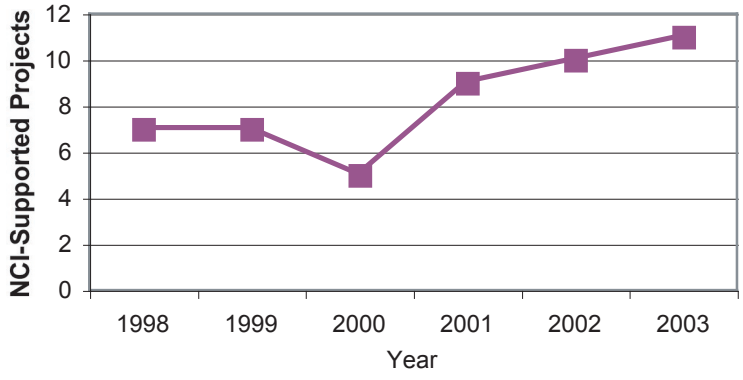


NCI Efforts:

- In FY2003, examples of active areas of investigation included a trial of aspirin and vitamin E in women.
- Examples of clinical trials addressing this priority included the following:
  - Phase I Study of Perillyl Alcohol in Women at Risk for Recurrent Breast Cancer (CCF-IRB-3574)
  - Phase II Randomized Chemoprevention Study of LY353381 Hydrochloride in Women With Fine Needle Aspiration Cytologic Evidence of Hyperplasia and at High Risk for Breast Cancer (KUMC-HSC-7264-97)
  - Phase II Randomized Study of Polyphenon E (Green Tea Extract) and Low-Dose Aspirin in Women at High Risk for Developing Breast Cancer (UCLA-0305011)
- An NCI initiative addressing this priority was Chemoprevention in Genetically-Identified High-Risk Groups: Interactive Research and Development Projects.

PRG Priority:

What is the efficacy of chemopreventive drugs in reducing breast cancer risk among women with inherited predisposition?[a]



NCI Efforts:

- In FY2003, examples of active areas of investigation included chemoprevention for women at high risk of breast cancer, new triterpenoids for chemoprevention of cancer, chemoprevention of breast and ovarian cancer, and biomarker modulation by COX-2 inhibitors.
- Examples of clinical trials addressing this priority included the following:
  - Phase I Study of Perillyl Alcohol in Women at Risk for Recurrent Breast Cancer (CCF-IRB-3574)
  - Phase II Chemoprevention Study of Celecoxib in Premenopausal Women at High Risk for Estrogen Receptor-Negative Breast Cancer (KUMC-HSC-8919-02)
  - Phase II Randomized Chemoprevention Study of LY353381 Hydrochloride in Women With Fine Needle Aspiration Cytologic Evidence of Hyperplasia and at High Risk for Breast Cancer (KUMC-HSC-7264-97)
  - Phase II Randomized Study of Polyphenon E (Green Tea Extract) and Low-Dose Aspirin in Women at High Risk for Developing Breast Cancer (UCLA-0305011)

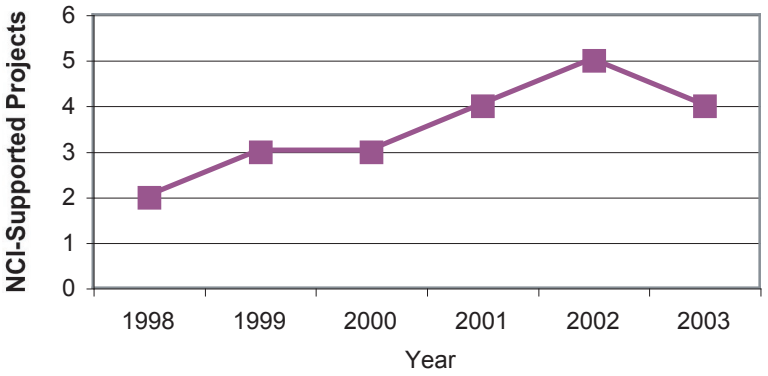
a This priority was part of the Genetics section in the original Breast Cancer PRG report.

- Randomized Chemoprevention Study of Bexarotene in Women at High Genetic Risk for Breast Cancer (BCM-H-9315)
- Phase III Randomized Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer (NASBP-P-2)

- On July 7-8, 1998, NCI sponsored the *Breast Cancer Prevention Trial (BCPT) Workshop*. On April 26-28, 2000, NCI sponsored the *NIH Selective Estrogen Receptor Modulators (SERMs) Workshop*. On December 11-12, 2000, NCI sponsored the U.S. Preventive Services Taskforce meeting.
- The NCI initiative addressing this priority was Chemoprevention in Genetically-Identified High-Risk Groups: Interactive Research and Development Projects.

PRG Priority:

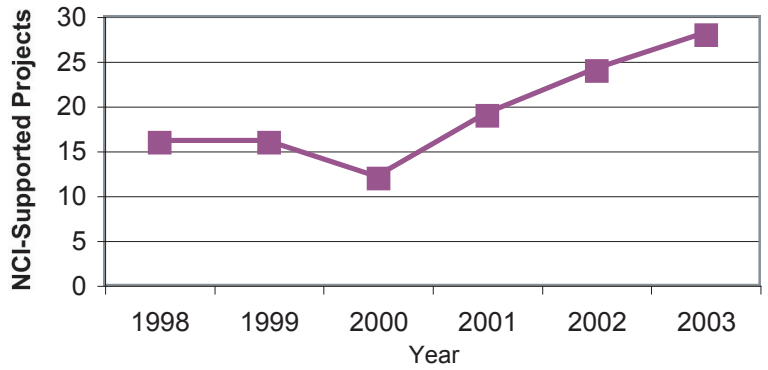
What is the efficacy of prophylactic mastectomy and prophylactic oophorectomy?[b]



NCI Efforts:

- In FY2003, examples of active areas of investigation included patient-oriented outcomes of prophylactic mastectomy, a prospective study of risk-reducing salpingo-oophorectomy and ovarian screening among women at increased genetic risk of breast and ovarian cancer, and the role of prophylactic surgery in reducing breast and ovarian cancer risk and mortality in BRCA1 and BRCA2 mutation carriers.

Additional Breast Cancer Prevention Projects



NCI Efforts:

- In FY2003, examples of active areas of investigation included cancer prevention in medical education practice, breast cancer risk assessment with Bayesian networks, p53 loss in human mammary epithelial cells as a model of breast cancer prevention, impact of mortality concerns on cancer risk behavior, and breast cancer prevention in female survivors of Hodgkin's disease.
- Active research projects in FY2003 related to reducing breast cancer health disparities included epidemiologic studies of diet and cancer in Hawaii, which explores etiologic factors for ethnic variations in cancer incidence and the study of energy balance and breast cancer in black and white women, which examines the relationship between energy balance and insulin resistance-related factors with the age-specific incidence of breast cancer in black and white women in the United States.

b This priority was part of the Genetics section in the original Breast Cancer PRG report.

Much of NCI's investment in breast cancer prevention research has focused on the identification of breast cancer risk factors and the evaluation of potential chemopreventive regimens for their ability to inhibit or delay the onset of clinical disease. The initiatives relevant to research on breast cancer prevention between 1998 and 2003 include the following list of general initiatives that are described in Table 2-1,[2] as well as the category-specific initiatives that are described in Table 5-2.[3]

- Aging Women and Breast Cancer
- Basic and Preclinical Research on Complementary Alternative Medicine (CAM)
- Breast and Ovarian Cancer Family Registries
- Breast Cancer Faculty
- Breast Cancer Surveillance Consortium (BCSC)
- Cancer Biomedical Informatics Grid (caBIG)
- Cancer Centers Program
- Cancer Genome Anatomy Project (CGAP)
- Cancer Molecular Analysis Project (CMAP)
- Cancer Research Small Grants Program
- Cancer Research Training, Career Development and Education Opportunities
- Clinical Trials Cooperative Group Program
- Community Clinical Oncology Program (CCOP)
- Competing Supplements for Organotypic Models of Cancer
- Cooperative Breast Cancer Tissue Resource (CBCTR)
- Cooperative Human Tissue Network (CHTN)
- Correlative Studies Using Specimens from Multi-Institutional Treatment Trials
- Director's Challenge: Toward a Molecular Classification of Tumors
- Exploratory Grants for Correlative Laboratory Studies and Clinical Trials
- Insight Awards to Stamp Out Breast Cancer
- Integrating Aging and Cancer Research
- Interdisciplinary Research Teams for Molecular Target Assessment
- *In Vivo* Cellular and Molecular Imaging Centers (ICMICs)
- Minority Institution/Cancer Center Partnership (MI/CCP)
- Minority-Based Community Clinical Oncology Program (MBCCOP)
- Molecular Target Drug Discovery for Cancer
- Mouse Models of Human Cancers Consortium
- NCI Center for Bioinformatics (NCICB)

2 Initiatives that impact multiple categories of breast cancer research.

3 Initiatives that are unique to this chapter on prevention.

- Shared Pathology Informatics Network (SPIN)
- Shared Resources for Scientists Outside NCI Cancer Centers
- Small Animal Imaging Resource Program (SAIRP)
- Southern Community Cohort Study
- Special Populations Networks
- Specialized Programs of Research Excellence (SPOREs) in Breast Cancer
- Specimen Resource Locator
- Therapeutic Modulation of Angiogenesis in Disease

Table 5-2. NCI Initiatives Relevant to Breast Cancer Research: Prevention[a]

Initiatives Focused on Breast Cancer

- Chemoprevention of Estrogen Receptor (ER)-Negative Breast Cancer Preclinical Studies (RFA-CA-03-005)
  - Overview: Supports the development and evaluation of preclinical chemopreventive strategies that could be rapidly translated to clinical studies and are applicable to women at high risk for development of ER-negative breast cancer.
  - Relevant Research Projects Resulting From This Initiative: Between 1998 and 2003, six projects relevant to breast cancer research were supported through this RFA. Specific projects can be found in Appendix B, Tables B2, B7, B10, B11, B14-16, and B19, by searching for the PA number.
- Study of Tamoxifen and Raloxifene (STAR) Trial (http://www.cancer.gov/star)
  - Overview: A major clinical trial with the goal of determining whether the osteoporosis drug raloxifene is as effective as tamoxifen in preventing breast cancer in postmenopausal women who are at high risk for developing breast cancer.
  - Relevant Resource Resulting From This Initiative: This project finished accrual in June 2004 of more than 19,000 volunteers who were randomized to use the intervention drug for a period of 5 years. Women from more than 400 sites across the United States, Puerto Rico, and Canada joined the effort. The Data and Safety Monitoring Committee for the trial will assess results on a periodic basis to determine when the conditions are met to publish results. The goal of the trial is to determine if raloxifene is comparable to tamoxifen in preventing breast cancer. If that is the case, then the preferred Selective Estrogen Receptor Modulator (SERM) for breast cancer prevention will be established on the basis of which agent has a more favorable risk-benefit profile. A full listing of STAR sites and important trial information, including updates, are available at the National Surgical Adjuvant Breast and Bowel Project (NASBP) Web site: www.nsabp.pitt.edu/.

Initiatives With Breast Cancer-Relevant Components

- Chemoprevention in Genetically-Identified High-Risk Groups: Interactive Research and Development Projects (RFA-CA-98-012)
  - Overview: Supports the establishment of integrated, multidisciplinary research programs that define and evaluate chemopreventive strategies in asymptomatic subsets of individuals at high risk for cancer.

a Lists of the projects derived from each initiative can be located on the online Supplement to the Breast Cancer Progress Report: Initiative Database.

- Relevant Projects Resulting From This RFA: Between 1998 and 2003, one project relevant to breast cancer research was supported through this RFA:

  Chemoprevention of Breast and Ovarian Cancer

- Phase I and II Cancer Prevention Clinical Trials Consortia (http://www.cancer.gov/newscenter/pressreleases/preventtrials)
  - Overview: Consortium of research centers designed to conduct early-phase cancer prevention clinical trials.
  - Relevant Resource Resulting From This Initiative: In 2003, six institutions were initially supported to conduct cancer prevention clinical trials to assess the potential of new agents. As part of the clinical trials, consortia members are expected to conduct studies on biological markers associated with cancer development and studies that elucidate mechanisms of cancer prevention. New consortium institutions include:

    University of Arizona

    University of California, Irvine

    Northwestern University

    Mayo Clinic Foundation

    University of Texas M. D. Anderson Cancer Center

    University of Wisconsin, Madison

- Rapid Access to Preventive Intervention Development (RAPID) Program (http://www3.cancer.gov/prevention/rapid/index.html)
  - Overview: Expedites the movement of novel molecules and concepts from the laboratory to the clinic for clinical trials of efficacy.
  - Relevant Research Projects Resulting From This Initiative: Since its inception in 2000, the RAPID program has provided assistance for 24 specific projects, which are listed on the RAPID Projects Web site. Three of these projects have direct relevance to breast cancer:

    Development of alpha-TEA, a Novel Tocopherol-Based Anticancer Agent, for Prevention of Breast Cancer Recurrence and Metastasis

    Preclinical Development of 9-cis-UAB30 for Breast Cancer Chemoprevention

    Preclinical Development of Four Flavonoids from Broussonetia papyrifera

Ongoing NCI Research: Recent Progress in Breast Cancer Prevention

Models of Precancerous Biology

NCI-supported research groups have developed valuable strains of mice that replicate various features of breast carcinogenesis in humans. These mouse models of breast carcinogenesis can be used to test the efficacy of chemopreventive agents. The *neu* transgenic mouse, which contains an activated form of the c-*neu* oncogene, develops estrogen receptor (ER)-negative breast tumors that resemble those found in approximately 25% of all women with breast carcinoma (Muller et al., 1988). These mice provide a useful animal model for the evaluation of intervention strategies to delay/prevent breast cancer and have been used to demonstrate the effectiveness of celecoxib (a COX-2 inhibitor) and gefitinib (an EGFR inhibitor) in the prevention of breast cancer (Howe et al., 2002, Lu et al., 2003). Likewise, conditional knockout of the BRCA-1 gene in the mammary epithelium

of mice also results in the formation of ER-negative mammary tumors that exhibit a host of other genetic alterations similar to those seen in human breast carcinomas (Xu et al., 1999; Brodie et al., 2001; Weaver et al., 2002). This model has been used to demonstrate the efficacy of prophylactic oophorectomy for the prevention of breast cancer and is currently being used to test a wide range of chemopreventive agents (Deng et al., 2004).

Dietary Factors

Several epidemiological studies suggest an association between the consumption of certain dietary components and a reduction in breast cancer risk. The mechanisms by which these components confer chemoprotection are diverse (e.g., carcinogen metabolism, cell division, apoptosis, differentiation, and hormonal homeostasis) and have become the focus of numerous NCI-sponsored research projects.

Various lines of evidence support the hypothesis that maintenance of a healthy body weight confers protection against postmenopausal breast cancer (Clinton et al., 1995). Moreover, a prospective population study found a significant positive linear trend in death rates for breast cancer with increasing body mass index (Calle et al., 2003). Although ecological and migrant studies usually demonstrate an association between fat intake and breast cancer, case-control and cohort studies have been inconsistent for this relationship (Kushi et al., 2002). In addition to quantity of fat consumed, the intake of specific fatty acids and duration of consumption may be involved in breast cancer (Rose, 1997). Interestingly, studies have identified several stages of a woman's life in which the mammary glands may be particularly sensitive to dietary factors (i.e., fat), including the prenatal phase, puberty, and pregnancy (Hilakivi-Clarke et al., 1999; Baer et al., 2003; Hilakivi-Clarke et al., 1996). The production, metabolism, and bioavailability of sex hormones and their impact on target tissues may be responsible for these effects, and it has been documented that a high-fat diet increases levels of circulating estrogens, thereby potentially increasing the risk of breast cancer (Longcope et al., 1987). Research shows that women may be able to reduce their levels of two types of estrogens, estradiol and estrone, by consuming soy foods daily or, potentially, the isoflavone components genistein and diadzen (Kumar et al., 2002; Lu et al., 2001). Recent evidence suggests that the benefit from soy foods may be dependent on time of exposure, with childhood exposures offering greatest response (Wu et al., 2002; Shu et al., 2001).

The NCI has sponsored research on the mechanisms of chemoprevention by other natural products that are associated with a reduction in breast cancer risk. For example, the green tea polyphenol epigallocatechin-3 gallate has been found to inhibit cell growth via Her2/*neu* oncoprotein inhibition in mammary tumor cells (Pianetti at al., 2002). Furthermore, upregulation and stimulation of the vitamin D receptor by vitamin D, the polyphenol resveratrol (found in red wine) and the phytoestrogen genistein (found in soy) can suppress breast cancer cell growth (Welsh et al., 2003).

Prevention Trials

NCI-sponsored clinical trials in breast cancer prevention have led to an increased understanding of breast cancer risk factors and effective strategies for the reduction of disease incidence in pre- and postmenopausal women. Current clinical trials address strategies to prevent primary breast cancers in high-risk patients as well as secondary malignancies in breast cancer survivors.

Several clinical trials are addressing the use of SERMs for the prevention of breast cancer in high-risk women. The Breast Cancer Prevention Trial, conducted by the NSABP, revealed a 49% reduction in breast cancer incidence among the high-risk participants taking tamoxifen versus those taking a placebo (Fisher et al., 1998). Although women taking tamoxifen were at a slightly greater risk for endometrial cancer, they were at no greater risk for heart attack and had fewer bone fractures of the hip, wrist, and spine than women taking the placebo. In 1998, the FDA approved tamoxifen for use by high-risk women for breast cancer chemoprevention. As a follow-up, the NSABP is conducting the Study of Tamoxifen and Raloxifene (STAR) trial to determine if the osteoporosis prevention drug raloxifene can reduce breast cancer incidence as well as tamoxifen, but with fewer side effects, in high-risk postmenopausal women. Approximately 19,000 volunteers are participating in this trial at more than 500 centers across the United States, Puerto Rico, and Canada.

Retinoids comprise another class of agents currently being investigated for breast cancer prevention. Retrospective analysis of data from one NCI-funded trial revealed that compared with untreated women, there were fewer second breast malignancies in premenopausal women, but not in postmenopausal women, randomized to the retinoid, fenretinide (Veronesi et al., 1999). In

addition, a significant decrease of circulating insulin-like growth factor (IGF)-1, a known risk factor for premenopausal breast cancer, was observed after 1 year of fenretinide administration in premenopausal women with breast cancer (Decensi et al., 2001). These results, along with preclinical studies of new generations of retinoids, support the continued evaluation of these compounds for the prevention of breast cancer, particularly among premenopausal women.

Continuing Needs and Evolution

The above summary of initiatives and accomplishments indicates that much progress has been made, but additional knowledge is needed to further reduce the incidence of breast cancer. The Breast Cancer Prevention Trial of tamoxifen in women at increased risk of breast cancer showed a 49% overall reduction in breast cancers in women who took tamoxifen for 5 years. ER-positive, invasive breast cancer cases were reduced by 70%; however, the tamoxifen intervention had little impact on the incidence of ER-negative breast cancer. Thus, an intervention strategy that reduces the incidence of both ER-positive and ER-negative breast cancer is a priority. Such a result might be achieved by combining a SERM with a second agent. As noted above, a number of small trials using such combinations are in progress, and mechanistic studies are under way to delineate the targets of suppression for pathways involved in both ER-positive and ER-negative disease.

In addition to the focus on targeted interventions, more specific methods of identifying breast cancer risk would greatly enhance the efficiency of definitive Phase III prevention trials, which currently require large numbers of women to be followed for many years. It is possible for a woman to enter a large trial like STAR if her risk of developing breast cancer over the 5 years from entry is 1.7% or more. A more reliable method for identifying women at risk would facilitate the conduct of large trials by reducing the number of participants required to enroll in the study.

Work is also being directed to determine why some of the women who use preventive interventions like tamoxifen develop breast cancer in spite of the intervention. For those women who are identified as eligible for an intervention to reduce breast cancer risk, a further goal is to reliably identify the subset of women who are most likely to benefit from the intervention. Targeted agents with increased specificity are expected to reduce unnecessary intervention.

Finally, it is a focus of prevention research to identify specific modifications of lifestyle, such as changes in diet and exercise patterns, which can be used to reduce breast cancer risk throughout life. This approach allows intervention at a much earlier stage of breast development for longer periods of time, avoiding some of the toxicities and cost that accompany pharmacologic interventions that are likely to be used later in life.

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Chapter 6:
Early Detection, Diagnosis, and Prognosis of Breast Cancer: NCI's Investment and Recent Progress

In the coming decade, we should strive to develop noninvasive methods for detecting and characterizing with certainty precancerous and cancerous breast lesions when they are small and more easily treated.
Charting the Course: Priorities for Breast Cancer Research

Research has shown that early detection, in combination with effective treatment, can reduce mortality from breast cancer. The steady drop in breast cancer mortality rates since the early 1990s has, to a great extent, been due to improvements in screening and treatment. NCI is supporting research on early detection to improve the technologies and practices of early screening and minimize the invasiveness of procedures. Research on diagnosis and prognosis is aimed at improving the accuracy of predictions regarding the course of disease and selecting the most appropriate interventions.

Recent research supported by NCI has identified many novel biomarkers for breast cancer, as well as new imaging technologies that may enhance mammography or serve as alternatives to it. For example, to develop and evaluate the feasibility of novel image acquisition or enhancement methods, NCI has issued a program announcement, Development of Novel Imaging Technologies, and is sponsoring the Diagnostic Imaging Network–American College of Radiology Imaging Network (ACRIN), a multi-institution network for cooperative studies. In addition, the Institute's Innovative Technologies for the Molecular Analysis of Cancer program supports the application of novel and emerging molecular analysis technologies in cancer research, including the identification of molecular markers. NCI's Exploratory Studies in Cancer Detection, Prognosis, and Prediction are exploring innovative strategies for the early detection of cancer, assessment of cancer prognosis, or prediction of response to cancer treatment.

In its 1998 report, the Breast Cancer PRG identified nine priorities that deal with important research topics in early detection, diagnosis, and prognosis of breast cancer. Five of these priorities address the need in cancer imaging to: determine the potential of newer imaging technologies to better detect and diagnose clinically significant breast disease, determine whether computer-aided technologies can further improve the interpretation of conventional mammography, identify the imaging characteristics of breast lesions detected by newer imaging technologies, develop standardized interpretation rules to identify these lesions using these modalities, determine whether early detection by any imaging modality truly changes the mortality from breast cancer, and develop new methods to diagnose clinically significant breast disease and predict clinical outcomes. Four of the PRG priorities focus on serum and tissue analyses: use tumor-specific biomarkers as functional imaging agents to improve the performance of imaging modalities; identify biomarkers that predict the clinical outcome of precancerous and cancerous breast lesions that are left untreated, as well as the response of precancerous and cancerous breast lesions to specific types of therapy; and interpret and use information on the complex phenotypes of breast lesions that involve abnormalities in many biomarkers simultaneously.

The NCI has been responsive to the PRG priorities related to the early detection, diagnosis, and prognosis of breast cancer. NCI-sponsored research has recently assessed the use of novel imaging technologies to serve as alternatives or adjuncts to mammography or to increase the sensitivity and specificity of mammography. Researchers have also identified numerous novel biologic markers that may serve as screening tests for the diagnosis and management of breast cancer, assess a patient's risk of developing an initial or secondary breast cancer, and predict the probable course of the disease and whether it will respond to a given therapy. Additionally, recent reports prepared by the Breast Screening Working Group and the Breast Cancer Surveillance Consortium evaluated screening practices and presented ongoing challenges and future opportunities to improve breast cancer screening (see Chapter 8 for more details).

NCI's Investment and Response

From FY1998 to 2003, NCI's extramural investment in breast cancer early detection, diagnosis, and prognosis research increased from $36.4 million to $73.2 million (Figure 6-1). This increase corresponds to increases in the number of projects that are responsive to the nine Breast Cancer PRG research priorities for early detection, diagnosis, and prognosis summarized in Table 6-1.[1]

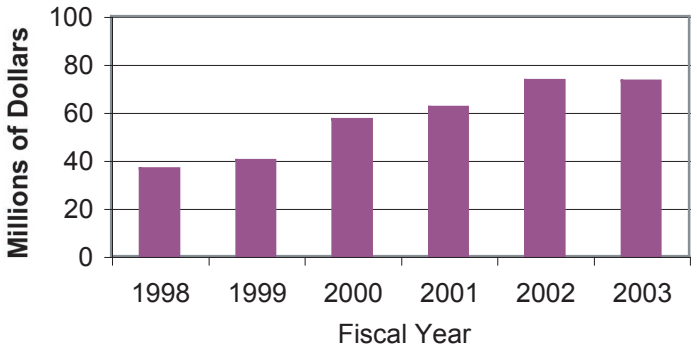
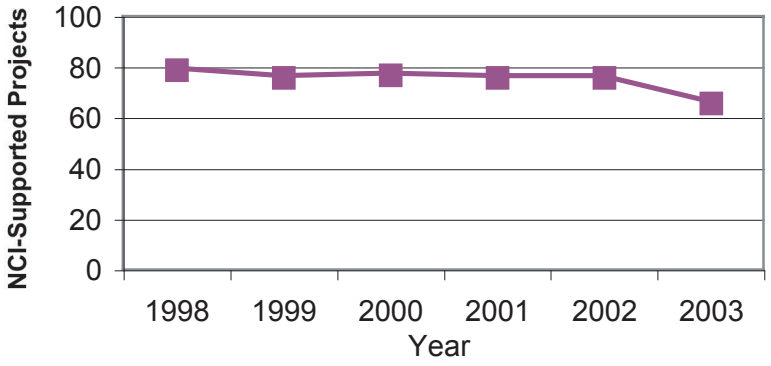


Figure 6-1. NCI's extramural investment in research on breast cancer early detection, diagnosis, and prognosis: 1998-2003 (in millions of dollars)

Table 6-1. NCI Efforts Responsive to PRG Priorities and Opportunities in Early Detection, Diagnosis, and Prognosis[a]

PRG Priority:

Determine the potential of newer imaging technologies (e.g., magnetic resonance imaging, positron emission tomography, digital mammography, mammoscintigraphy, sentinel lymph node localization/sampling, magnetic resonance elastography, electrical impedance imaging, microwave spectroscopy, and near-infrared spectroscopy) to detect and diagnose clinically significant breast disease better than is currently done by physical examination and conventional mammography.



NCI Efforts:

- In FY2003, examples of active areas of investigation included positron emission tomography (PET) cameras with optimized geometry for detecting breast cancer or axillary node involvement, an integrated ultrasound and digital x-ray imaging system for screening and diagnostic mammography, breast cancer metabolic imaging with near-infrared light, and analytical solution techniques to improve magnetic resonance elastography.
- Examples of clinical trials addressing this priority included the following:
  - Comparison of Positron Emitter Iodine I 124 Iododeoxyuridine with Fludeoxyglucose F 18 (F-18 2-Fluoro-2-Deoxy-(D)-Glucose) as Tracer for Glycolysis on Scans and in Tumor Samples in Patients With Advanced Breast Cancer (MSKCC-97046)

a. Some of the original PRG priorities are addressed jointly in Table 6-1 because these priorities address partially overlapping issues and they are relevant to many of the same research projects and initiatives.

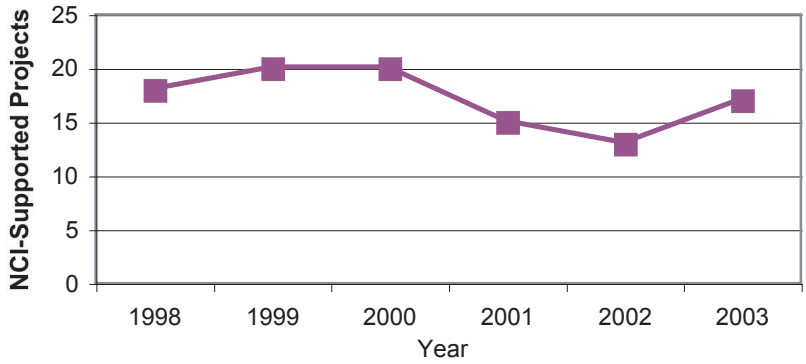
1 A project may map to more than one PRG priority and therefore be represented in more than one figure. Projects active in 2003 are listed in Appendix B (Tables B-24 to B-32) by Principal Investigator's name for each PRG priority.

- Diagnostic Study of Magnetic Resonance Imaging in Evaluating the Contralateral Breast of Women with a Recent Unilateral Diagnosis of Breast Cancer (ACRIN-6667)
- Randomized Screening and Diagnostic Study of Digital Mammography Versus Screen-Film Mammography in the Detection of Breast Cancer in Women (ACRIN 6652)
- Pilot Diagnostic Study of Fludeoxyglucose F 18 Positron Emission Tomography for Preoperative Evaluation of Women with Primary or Recurrent Breast Cancer (MSKCC-01134)
- Screening Study of Breast Imaging Outcome Measures and Phase of Menstrual Cycle in Women at High Genetic Risk of Breast Cancer (NCI-01-C-0008)

- On September 26, 2002, NCI sponsored the *Third Inter-Institute Workshop on Diagnostic Optical Imaging and Spectroscopy: The Clinical Adventure*. On February 6-7, 2003, NCI sponsored the *4th National Forum on Biomedical Imaging in Oncology*.
- NCI initiatives addressing this priority included the Bioengineering Research Grants, Breast Specialized Programs of Research Excellence (SPOREs), Cancer Imaging Program (CIP), Development of Novel Technologies for *In Vivo* Imaging, and Diagnostic Imaging Network—American College of Radiology Imaging Network (ACRIN).

PRG Priority:

Can computer-aided technologies further improve the interpretation of conventional mammography?

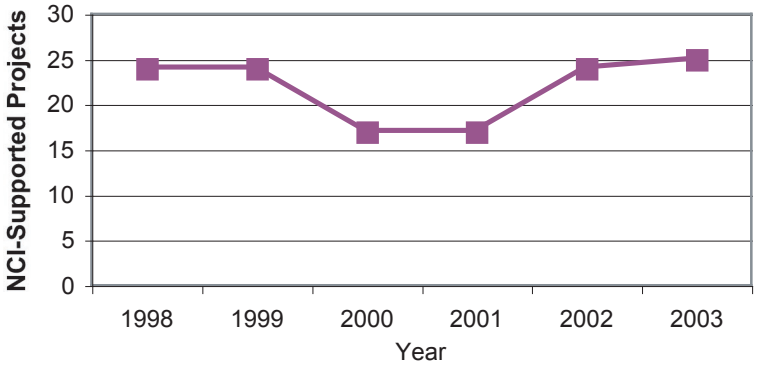


NCI Efforts:

- In FY2003, examples of active areas of investigation included studies to improve and test the performance and robustness of several computer-aided diagnosis (CAD) schemes for mammography; a content-based search engine that displays lesions of known pathology, making artificial neural network (ANN) output more reliable for computer processing; and CAD methodology for extracting information related to the spatial structure of the breast from ipsilateral views.
- Examples of clinical trials addressing this priority included the following:
  - Randomized Screening and Diagnostic Study of Digital Mammography Versus Screen-Film Mammography in the Detection of Breast Cancer in Women (ACRIN-6652)
  - Screening and Diagnostic Study of Magnetic Resonance Imaging in Women with Suspected Breast Cancer (UPCC-ACR-6884)
  - Diagnostic Study of Magnetic Resonance Imaging in Women With Suspected Breast Tumors (UPCC-ACR-6883).
- On September 26, 2002, NCI sponsored the Third Inter-Institute Workshop on Diagnostic Optical Imaging and Spectroscopy: The Clinical Adventure. On February 6-7, 2003, NCI sponsored the 4th National Forum on Biomedical Imaging in Oncology
- NCI initiatives addressing this priority included the Cancer Imaging Program, Development of Novel Technologies for *In Vivo* Imaging, Diagnostic Imaging Network—American College of Radiology Imaging Network (ACRIN), and Exploratory/Developmental Grants for Diagnostic Cancer Imaging.

PRG Priority:

What are the imaging characteristics of specific types of benign and malignant breast lesions detected by newer imaging technologies? Can standardized interpretation rules be developed to identify these lesions for any of these modalities? Can they replace or augment conventional mammography in screening general or high-risk populations?

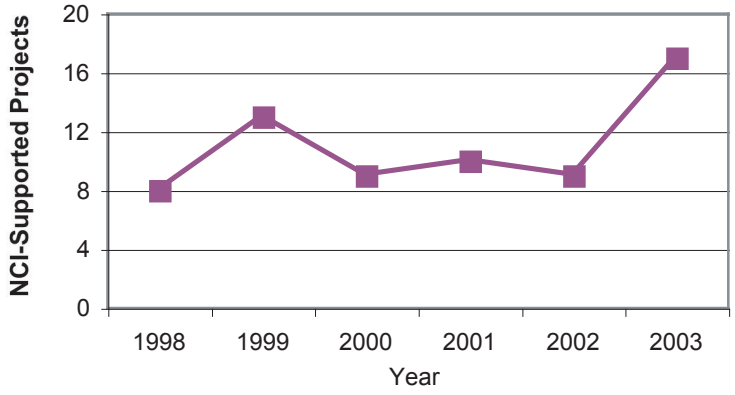


NCI Efforts:

- In FY2003, examples of active areas of investigation included computer models that combine mammography and breast ultrasound findings to identify breast masses that are probably benign; a unilateral method of obtaining rapid dynamic and high-spatial-resolution, contrast-enhanced breast MRI data; the integration of gray-scale ultrasound and Doppler imaging to diagnose breast cancers; and the use of thermal information as an adjunct to mammography for equivocal mammography results.
- Examples of clinical trials addressing this priority included the following:
  - Radiolabeled 99mTechnetium-Dextran (99Tcm-Dextran) With Isosulfan Blue Prior to Resection of the Sentinel Lymph Node in Breast Cancer Patients (UCLA-HSPC-960629301)
  - Diagnostic Study of Positron Emission Tomography in Patients With Stage II-IV or Recurrent Breast Cancer (NCI-94-C-0151)
  - Pilot Screening Study of Breast Imaging Outcome Measures in Women at High Genetic Risk of Breast Cancer (NCI-01-C-0009)
- On February 6-7, 2003, NCI sponsored the *4th National Forum on Biomedical Imaging in Oncology*.
- NCI initiatives addressing this priority included the Cancer Imaging Program (CIP), the Cancer Research Network (CRN), and Diagnostic Imaging Network—American College of Radiology Imaging Network (ACRIN).

PRG Priority:

Can tumor-specific biomarkers be identified and used as imaging agents to improve the performance of any imaging modality?[b]



NCI Efforts:

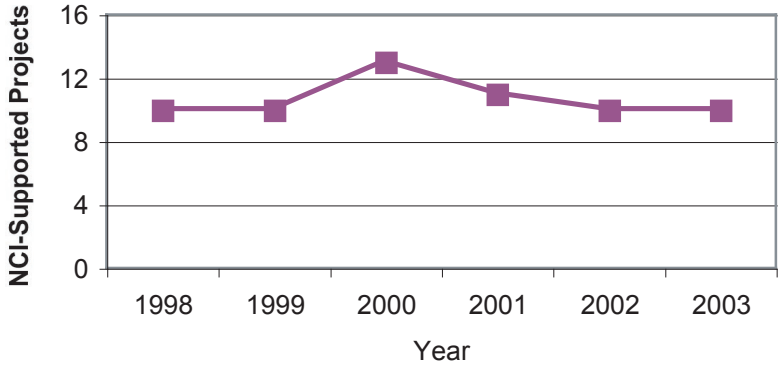
- In FY2003, examples of active areas of investigation included near-infrared-emitting, fluorochrome-conjugated metabolite probes capable of imaging *in vivo* metabolic function in real time, monitoring tumor neovascularity using contrast-enhanced ultrasound imaging modes, estrogens labeled with fluorine-18 and carbon-11 as imaging agents for estrogen receptor-positive tumors, and near-infrared-fluorescent contrast agents and optical imaging for sentinel lymph node mapping *in vivo*.

b The priority was changed from the original "Can tumor-specific biomarkers be identified and used as contrast agents to improve the performance of any imaging modality?"

- NCI initiatives addressing this priority incl;uded the Cancer Imaging Program (CIP), the Cancer Research Small Grant Program, the Early Detection Research Network, and *In Vivo* Cellular and Molecular Imaging Centers (ICMICs).

PRG Priority:

Does early detection by any imaging modality truly change the mortality from breast cancer?

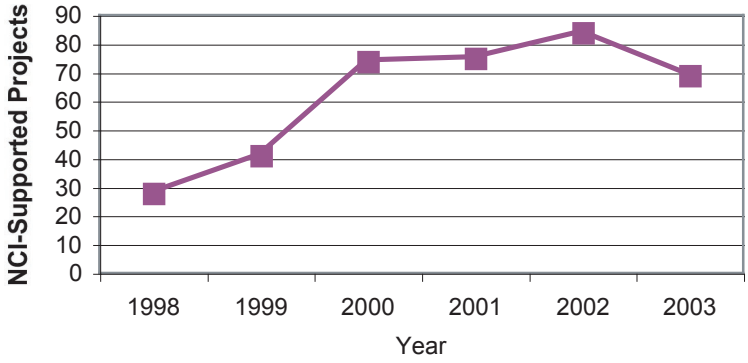


NCI Efforts:

- In FY2003, examples of active areas of investigation included several long-term data collection and linkage efforts to measure the accuracy and outcomes of screening mammography.
- The NCI initiative addressing this priority was the International Breast Cancer Screening Network (IBSN).

PRG Priority:

Develop new methods to diagnose clinically significant breast disease and predict clinical outcomes better than conventional histologic examination and the few available biomarker assays (e.g., S-phase fraction, estrogen receptor, progesterone receptor, and c-erbB-2).



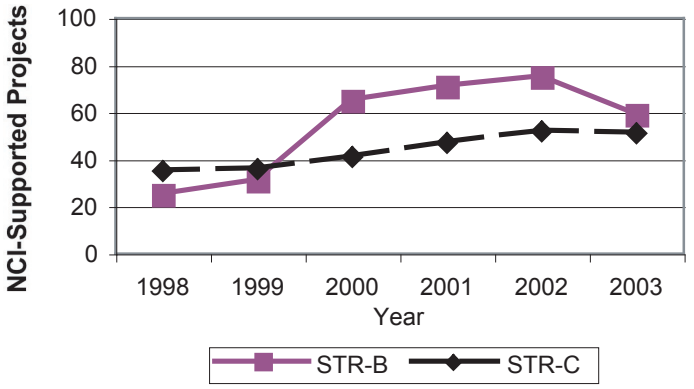
NCI Efforts:

- In FY2003, examples of active areas of investigation included radiolabeled gastrin-releasing, peptide receptor-avid radiopharmaceuticals as site-directed agents to treat and/or diagnose patients with breast cancer; a novel DNA chip for high-throughput analysis of promoter hypermethylation in primary tumors; microchip electrophoresis technologies for molecular detection of cancer by tandem single-strand conformational polymorphism/heteroduplex analysis; and multimarker, real-time reverse transcriptase-polymerase chain reaction (RT-PCR) detection of breast cancer cells in lymph nodes of breast cancer patients to detect metastases.
- Examples of clinical trials addressing this priority included the following:
  - Diagnostic Randomized Study of Radioactive Seed Localized Breast Biopsy Versus Needle Localized Breast Biopsy in Patients with Nonpalpable Breast Lesions (MCC-12114)
  - Pilot Study to Evaluate the Incidence of Clonal Hematopoiesis as a Marker of Genetic Damage Following Adjuvant Chemotherapy for Stage II/III Breast Cancer (SWOG-S9719)
- On January 7-8, 2002, NCI sponsored a workshop, *Detection and Measurement of Occult Disease for the Prognosis of Solid Tumors*, to identify priorities for new clinical studies.
- NCI initiatives addressing this priority included Applications of Innovative Technologies for the Molecular Analysis of Cancer; the Breast SPOREs; Cancer Prognosis and Prediction; Clinical Proteomics Program (CPP); Early Detection Research Network; Exploratory Studies in Cancer Detection, Prognosis, and Prediction; Exploratory/Developmental Grants for Diagnostic Cancer Imaging; Cancer Diagnosis Program; and Program for the Assessment of Clinical Cancer Tests.

PRG Priorities:

Are there biomarkers that predict the clinical outcome of precancerous and cancerous breast lesions if left untreated (i.e., prognostic factors) with a high degree of certainty? (STR-B)

Are there biomarkers that predict the response of precancerous and cancerous breast lesions to specific types of therapy (i.e., predictive factors) with a high degree of certainty? (STR-C)



NCI Efforts:

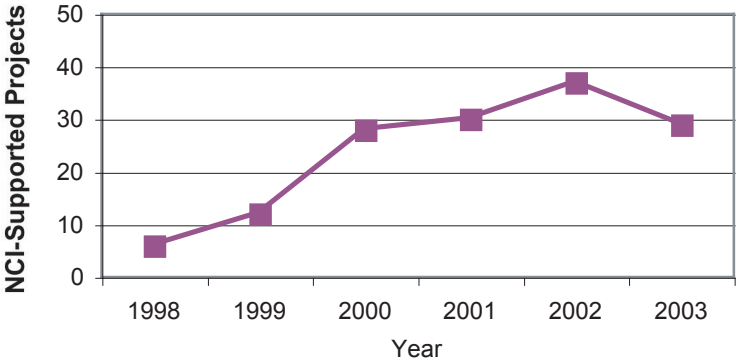
- In FY2003, examples of active areas of investigation relevant to the following priorities included:
  - Both STR-B and STR-C: the development of markers of apoptosis and cell proliferation, a probe for accurate sentinel node localization without the need for the radioactive technetium tracer, *in vivo* measurements of tumor metabolism to predict and evaluate response to therapy, a comprehensive gene expression profile to compare sets of lymph node-negative breast cancer, and an evaluation of the perinucleolar compartment as a prognostic and predictive tumor marker.
  - STR-B: the angiogenesis status in invasive ductal carcinoma of the breast by immunohistochemistry and magnetic resonance imaging (MRI), changes in the apparent diffusion coefficient of tissue water in response to chemotherapy as a marker for apoptosis, and probes as imaging agents for the epidermal growth factor receptor (EGFR).
  - STR-C: cancer chemoprevention by a set of phytochemicals, quantitative analysis of the expression of the molecule Her2/*neu* on breast tissue biopsies, and a functional cloning strategy to identify Taxol resistance-inducing genes.
- Examples of clinical trials addressing these priorities included the following:
  - Diagnostic Study of Contrast-Enhanced Magnetic Resonance Imaging and Correlative Molecular Studies in Women With Locally Advanced Breast Cancer Who Are Receiving Neoadjuvant Chemotherapy (CALGB-150007)
- On October 14-16, 2001, NCI's Cancer Biomarkers Research Group sponsored the *2nd Annual Scientific Workshop of the Early Detection Research Network* (EDRN). On January 7-8, 2002, NCI sponsored a workshop, *Detection and Measurement of Occult Disease for the Prognosis of Solid Tumors*, to identify priorities for new clinical studies.
- NCI initiatives addressing this priority included the Breast SPOREs; Cancer Prognosis and Prediction; Clinical Proteomics Program (CPP); Early Detection Research Network; Exploratory Studies in Cancer Detection, Prognosis, and Prediction; Cancer Diagnosis Program; and Program for the Assessment of Clinical Cancer Tests.

PRG Priority:

Premalignant and malignant breast lesions often have complex phenotypes involving abnormalities in many biomarkers simultaneously. How do we interpret and use this information?

NCI Efforts:

- In FY2003, examples of active areas of investigation included imaging probes for the *in vivo* sensing of specific proteases, molecular

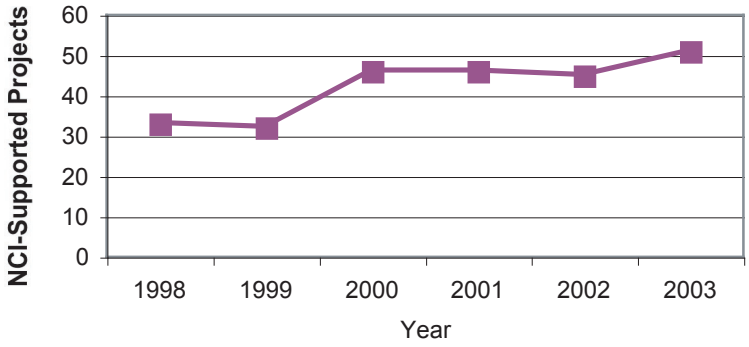


diagnostic tests for breast cancer, prognostic modeling for patients with high-risk primary breast cancer, and assays using expression-based markers to detect circulating breast cancer cells.

- Examples of clinical trials addressing these priorities included the following:
  - Diagnostic and Genetic Study of Breast Duct Lavage, Breast Duct Endoscopy, and DNA Gene Expression Profiling in Women With Ipsilateral Breast Cancer Versus Healthy Women Who Are Not at High Risk for Breast Cancer (NCI-02-C-0077B)
  - Phase II Pilot Study of cDNA Microarray as a Measure of Tumor Response to Neoadjuvant Docetaxel and Capecitabine Followed by Surgery and Adjuvant Doxorubicin and Cyclophosphamide in Patients With Stage II or III Breast Cancer (NCI-00-C-0149)
- On October 14-16, 2001, NCI's Cancer Biomarkers Research Group sponsored the *2nd Annual Scientific Workshop of the Early Detection Research Network* (EDRN). On January 7-8, 2002, NCI sponsored a workshop, *Detection and Measurement of Occult Disease for the Prognosis of Solid Tumors*, to identify priorities for new clinical studies.
- NCI initiatives addressing this priority included the Breast SPOREs; Cancer Prognosis and Prediction; Clinical Proteomics Program (CPP); Early Detection Research Network; Exploratory Studies in Cancer Detection, Prognosis, and Prediction; Cooperative Breast Cancer Tissue Resource; Cancer Diagnosis Program; Program for the Assessment of Clinical Cancer Tests; and Director's Challenge: Toward a Molecular Classification of Tumors.

Additional Breast Cancer Early Detection, Diagnosis, and Prognosis Projects

NCI Efforts:



- In FY2003, examples of active areas of investigation included biological markers of breast cancer and tamoxifen response; mammaglobin, a breast-specific gene, as a marker for the detection of breast cancer; a diagnostic device that measures optical and electrical properties of tissue near the tip of a 20-gauge needle probe; and an integrated model of disease history linked to submodels portraying modifiable points in the cancer control process, including early detection and methods to enhance diagnosis.

The initiatives relevant to research on breast cancer early detection, diagnosis, and prognosis between FY1998 and 2003 include the following list of general initiatives that are described in Table 2-1[2] (Chapter 2) and the category-specific initiatives that are listed and described in Table 6-2:[3]

- Aging Women and Breast Cancer
- Applications of Innovative Technologies for the Molecular Analysis of Cancer
- Bioengineering Research Grants
- Bioengineering Research Partnerships

2 Initiatives that impact multiple categories of breast cancer research.

3 Initiatives that are unique to the early detection, diagnosis, and prognosis research category.

- Breast and Ovarian Cancer Family Registries (CFRs)
- Breast Cancer Faculty
- Breast Cancer Surveillance Consortium (BCSC)
- Cancer Biomedical Informatics Grid (caBIG)
- Cancer Centers Program
- Cancer Genome Anatomy Project (CGAP)
- Cancer Imaging Program (CIP)
- Cancer Molecular Analysis Project (CMAP)
- Cancer Prognosis and Prediction
- Cancer Research Network (CRN)
- Cancer Research Small Grant Program
- Cancer Research Training, Career Development, and Education Opportunities
- Clinical Trials Cooperative Group Program
- Cooperative Breast Cancer Tissue Resource (CBCTR)
- Cooperative Human Tissue Network (CHTN)
- Correlative Studies Using Specimens From Multi-Institutional Treatment Trials
- Director's Challenge: Toward a Molecular Classification of Tumors
- Exploratory Grants for Correlative Laboratory Studies and Clinical Trials
- Improving DNA, RNA and Protein Availability in Fixed Tissue
- Insight Awards to Stamp Out Breast Cancer
- Integrating Aging and Cancer Research
- Interdisciplinary Research Teams for Molecular Target Assessment
- International Breast Cancer Screening Network
- *In Vivo* Cellular and Molecular Imaging Centers (ICMICs)
- Minority Institution/Cancer Center Partnership (MI/CCP)
- NCI Center for Bioinformatics (NCICB)
- Program for Assessment of Clinical Cancer Tests (PACCT)
- Shared Pathology Informatics Network (SPIN)
- Shared Resources for Scientists Outside NCI Cancer Centers
- Small Animal Imaging Resource Program (SAIRP)
- Small Grants Program for Cancer Epidemiology
- Specialized Programs of Research Excellence (SPOREs) in Breast Cancer
- Specimen Resource Locator

- Technologies for Comprehensive, Sensitive, and Quantitative Protein Analysis in Human Tumors
- Therapeutic Modulation of Angiogenesis in Disease
- Unconventional Innovations Program (UIP)

Table 6-2. NCI Initiatives Relevant to Breast Cancer Research: Early Detection, Diagnosis, and Prognosis[a]

Initiatives Relevant to Breast Cancer Research

- Development of Digital Mammography Displays and Workstations (PA-99-082; PA-99-083)
  - Overview: Supports advances in the state of the art in digital mammography displays and workstation design to obtain the full potential of digital mammography for improved breast cancer diagnosis.
  - Relevant Research Projects Resulting From This PA: Between 1998 and 2003, five projects relevant to breast cancer research were supported through this PA. One of these projects was active in 2003 and can be found in Appendix B, Table B24, by searching for the PA number.

Initiatives with Breast Cancer-Relevant Components

- Cancer Diagnosis Program (http://www.cancerdiagnosis.nci.nih.gov/)
  - Overview: Stimulates and supports diagnostics research, resources, and improved technologies to guide the choice of treatment for cancer patients.
  - Relevant Projects Resulting From This Initiative:

    Breast Cancer Diagnosis: Blood-Cell Multigene Signatures

    The Perinucleolar Compartment as Breast Cancer Marker

    Multimarker Detection of Breast Metastases in PET Nodes

    Prognostic Modeling of High-Risk Primary Breast Cancer
- Clinical Proteomics Program (CPP) (http://ncifdaproteomics.com/index.php)
  - Overview: Facilitates the invention, development, and employment of proteomic technologies for translational bench-to-bedside cancer treatment applications. CPP is supported by both the NCI and U.S. Food and Drug Administration.
  - Relevant Technologies Resulting From This Initiative: The CPP strives to improve early cancer detection technologies and develop new approaches to more effectively determine product safety, potency, and purity. Two exciting new technologies have been developed:

    Reverse-Phase Protein Microarrays for Signal Pathway Profiling and Phosphoproteomics

    Serum Proteomic Pattern Diagnostics for Blood-Based Detection of Cancer
- Development of Clinical Imaging Drug Enhancers (DCIDE) (http://www3.cancer.gov/bip/DCID_des.htm)
  - Overview: Expedites and facilitates the development of promising investigational imaging enhancers (contrast agents) or molecular probes from the laboratory to Investigational New Drug status.
  - Relevant Products Resulting From This Initiative: New imaging reagents for PET and MRI detection of tumor angiogenesis are being evaluated.

a. Lists of the projects derived from initiatives can be found on the online Supplement to the Breast Cancer Progress Report: Initiative Database.

- Development of Novel Technologies for *In Vivo* Imaging (PAR-01-101; PAR-01-102)
  - Overview: Facilitates the development of novel imaging technologies for early detection, screening, diagnosis, or image-guided treatment of cancer and environmentally induced disease, as well as clinical evaluation studies that are limited to proof of concept.
  - Relevant Research Projects Resulting From These PAs: Between 1998 and 2003, 27 projects relevant to breast cancer research were supported through these PAs. Specific projects can be found in Appendix B, Tables B24-B27, B29, B30, and B33, by searching for these and the previously issued PA numbers (PAR-00-089 and PAR-00-090).
- Diagnostic Imaging Network–American College of Radiology Imaging Network (ACRIN) (http://www.acrin.org/)
  - Overview: Facilitating cooperative studies in diagnostic imaging. ACRIN is a multi-institutional network that is developing productive interfaces with industrial sources of new imaging technologies and has the capacity to perform pilot studies and randomized, controlled trials to assess the value of imaging innovations in the practice of oncology.
  - Relevant Clinical Trials Resulting From This Initiative: Current clinical protocols are published on the ACRIN Web site and include four breast cancer trials:

    Contrast-Enhanced Breast MRI for Evaluation of Patients Undergoing Neoadjuvant Treatment for Locally Advanced Breast Cancer

    Digital Versus Film-Screen Mammography

    MRI Evaluation of the Contralateral Breast in Women With a Recent Diagnosis of Breast Cancer

    Screening Breast Ultrasound in High-Risk Women
- Early Detection Research Network (EDRN) (http://www3.cancer.gov/prevention/cbrg/edrn)
  - Overview: Collaboratively develops and tests promising biomarkers and technologies, with rapid dissemination of results. The consortium currently includes: 18 biomarker development laboratories, with 4 that address breast cancer; 3 biomarker validation laboratories; 9 clinical and epidemiologic centers, with 1 that addresses breast cancer, and a single data management and coordinating center. The EDRN organization includes a Breast and Gynecologic Cancer Collaborative Group.
  - Relevant Projects Resulting From This Initiative: Between 1998 and 2003, six projects relevant to breast cancer research were supported through this initiative. Specific projects can be found in Appendix B, Tables B2, B7, B9, B15, and B29-B31, by searching for the RFA number (RFA-CA-98-028).
- Exploratory/Developmental Grants for Diagnostic Cancer Imaging (PA-01-030)
  - Overview: Supports highly innovative research concepts in diagnostic cancer imaging.
  - Relevant Research Projects Resulting From This PA: Between 1998 and 2003, 35 projects relevant to breast cancer research were supported through this PA. Specific projects can be found in Appendix B, Tables B24-B27, B29, and B33, by searching for this PA number and the previously issued PA number (PA-98-008).
- Exploratory Studies in Cancer Detection, Prognosis and Prediction (PA-03-003)
  - Overview: Promotes the initial evaluation of molecular or cellular characteristics in human specimens and/or the development of assays that may result in important advances in the detection, diagnosis, and treatment of cancers.
  - Relevant Research Projects Resulting From This PA: Between 1998 and 2003, eight projects relevant to breast cancer research were supported through this PA. Specific projects can be found in Appendix B, Tables B2, B4, B7, B9, B15, B29-B31, and B36, by searching for the PA number and the previously issued PA number (PA-01-010).

- Exploratory Studies in Cancer Diagnostics (PA-98-022)
  - Overview: Provides support for research to identify novel molecular or cellular abnormalities in tumors that will be useful for cancer diagnosis.
  - Relevant Research Projects Resulting From This PA: Between 1998 and 2003, nine projects relevant to breast cancer research were supported through this PA.[b]
- Gene Expression Data Portal (GEDP) (http://gedp.nci.nih.gov/dc/index.jsp)
  - Overview: Facilitates microarray research through publicly available online data annotation and analysis tools and stores microarray data for sharing with the research community.
  - Relevant Research Products Maintained through This Initiative: Relevant data are available for the following research areas:

    Multiclass Cancer Diagnosis Using Tumor Gene Expression Signatures

    Initiating Oncogenic Event Determines Gene-Expression Patterns Of Human Breast Cancer Models

    Initiating Oncogenic Events Determines Gene-Expression Patterns Of Breast Cancer Models–C3(1)/SV40Tag

    Initiating Oncogenic Events Determines Gene-Expression Patterns Of Breast Cancer Models–MMTV-c-myc

    Initiating Oncogenic Events Determines Gene-Expression Patterns Of Breast Cancer Models–MMTV-HA-ras

    Initiating Oncogenic Events Determines Gene-Expression Patterns Of Breast Cancer Models–MMTV-neu

    Initiating Oncogenic Events Determines Gene-Expression Patterns Of Breast Cancer Models–MMTV-PyMT

    Initiating Oncogenic Events Determines Gene-Expression Patterns Of Breast Cancer Models–WAP-SV40(Tag)

    Secretory Activation in Wild-Type Mice From Preg12 to Lac9
- Innovative Technologies for the Molecular Analysis of Cancer (PAR-01-105; PAR-01-104)
  - Overview: Supports development of novel technologies for the molecular analysis of cancers and their host environment through basic, clinical, and epidemiological research.
  - Relevant Research Projects Resulting From These PAs: Between 1998 and 2003, 34 projects relevant to breast cancer research were supported through these PAs. Specific projects can be found in Appendix B, Tables B1-B3 and B29-B32, by searching for these and the previously issued PA numbers (PAR-98-066, PAR-98-067, PAR-99-100, and PAR-99-101).
- Tissue Array Research Program (TARP) (http://ccr.cancer.gov/tech_initiatives/tarp)
  - Overview: Develops and disseminates Multi-Tumor Tissue Microarray slides and related technology to cancer research investigators.
  - Relevant Resource Resulting From This Initiative: TARP distributes a Breast and Ovarian Cancer Array containing 65 well-annotated breast adenocarcinoma samples that can be used for immunofluorescence, *in situ* hybridization, immunohistochemistry, and histochemistry applications. Related protocols are also available on the TARP Web site.

b. Lists of the projects derived from initiatives can be found on the online Supplement to the Breast Cancer Progress Report: Initiative Database.

Ongoing NCI Research: Recent Progress in Breast Cancer Early Detection, Diagnosis, and Prognosis

Imaging Technologies

Breast cancer screening and detection methods have improved as technological advances have occurred. Novel imaging devices are now available in digital formats that can be read, analyzed, stored, and shared by health care providers.

One alternative to mammography that is currently being investigated is PET, a molecular imaging method that provides information on a tumor's biology using radioactive tracers to evaluate viability and glucose metabolism (using fluoro-deoxy-glucose [FDG]), oxygen status, and estrogen receptor status. In a recent prospective multicenter study on the role of FDG-PET in axillary node staging, researchers found that FDG-PET is moderately accurate for detecting axillary metastasis although false-negative axillae resulted from nodal metastases being smaller and fewer in number than true-positive axillae (Wahl et al., 2004). PET techniques are being used to evaluate the changes in blood flow and metabolism in locally advanced breast cancer following neoadjuvant therapy (Mankoff et al., 2003). PET has also been used for detecting increased tumor uptake of FDG to predict whether patients with estrogen receptor (ER)-positive metastatic breast cancer will respond to antiestrogen therapy (Dehdashti et al., 1999).

Another technology, MRI, is being used increasingly to characterize suspicious breast lesions detected on mammography and to monitor response to therapy. Although contrast-enhanced MRI has high sensitivity, its signal characteristics are not quite specific for cancer. Researchers are therefore exploring the possibility of developing and using a tissue signature method for identification and classification of normal and abnormal breast tissue (Jacobs et al., 2003). The use of MRI to evaluate response of breast cancer to hormonal therapy is also under investigation (Bogin and Degan, 2002). Furthermore, researchers are using streptavidin-conjugated superparamagnetic nanoparticles as targeted MR functional imaging agents to conduct cellular studies of the Her2/*neu* receptor, which plays a significant role in staging and treating breast cancer (Artemov et al., 2003).

Computers are being used as analytic and knowledge-enhancing tools to improve the diagnostic accuracy of breast imaging. For example, investigators have evaluated the effectiveness of a convolution neural network (CNN) optimized with an automated technique to improve the accuracy of a microcalcification detection computer program, in comparison with manually selected CNN. The sensitivity for the optimized CNN was 93%, compared with 87% for the manually selected CNN. The authors concluded that an optimized CNN can reduce false-positive findings and improve the accuracy of a computer-aided detection system (Gurcan et al., 2002).

Investigators have also analyzed an automated estimation analysis tool to estimate mammographic breast density (Zhou et al., 2001). The computer misclassified only 6% of the breast regions and produced highly accurate results for the remaining mammograms. This technique might be useful for estimating risk or for monitoring breast density changes in prevention or intervention programs.

Biologic Markers

As a result of powerful new molecular technologies, studies of biologic markers have significantly increased. Biologic markers have been detected in human serum, breast nipple aspirate fluid, and tissue samples. The following NCI-supported research represents examples of biologic markers for breast cancer that may become clinically useful.

The mammaglobin gene encodes a 10 kDa glycoprotein, and in normal adult tissues, mammaglobin mRNA expression has been detected only in the mammary gland. Researchers found that 80% of all primary and metastatic breast tumors were strongly immunopositive for mammaglobin protein, and staining was independent of tumor grade (Fleming and Watson, 2000). When researchers used a monoclonal antibody-based assay to monitor the presence of mammaglobin in serum, they found elevated levels in sera of patients with breast cancer compared to the sera of healthy women (Fanger et al., 2002). These results indicate that mammaglobin protein and mRNA in clinical samples might be useful markers for primary, metastatic, and occult breast cancer and that mammaglobin might provide a rapid screening test for the diagnosis and management of breast cancer.

The epidermal growth factor receptor (EGFR) family of growth factor receptor tyrosine kinases includes EGFR and ErbB-2, which is overexpressed in about one-third of breast cancers. ErbB-2 and EGFR may mediate motility through signaling that enables changes in the actin cytoskeleton, and this motility may depend on the coexpression of gelsolin, an actin-binding protein. When the expression of ErbB-2, EGFR, and gelsolin was analyzed in archival invasive breast cancers, researchers found that tumor gelsolin was associated with overexpression of ErbB-2 and EGFR, as well as an aggressive tumor phenotype (Thor et al., 2001). Gelsolin coexpression might be an important prognostic factor in patients with ErbB-2-positive, EGFR-negative breast cancer.

2,6-cyclolycopene-1,5-diol is the major oxidation product of lycopene in human serum. Researchers used high-performance liquid chromatography with electrochemical detection to quantify 2,6-cyclolycopene-1,5-diol and lycopene in plasma and breast nipple aspirate fluid (NAF). Levels of 2,6-cyclolycopene-1,5-diol and 8-isoprostane (a marker of lipid oxidation) were higher in NAF than in plasma and are consistent with high levels of oxidative stress in the breast (Chen and Djuric, 2002). Therefore, oxidized lycopene metabolites may serve as markers of oxidative stress.

Combinations of markers are now proving to be stronger predictors of recurrence than single markers. Examination of gene expression using cDNA microarrays has resulted in the identification of clusters of expressed genes that are associated with different types of breast tumors (Perou et al., 2000) and with risk of recurrence (Sorlie et al., 2001). These data have been used to develop an RT-PCR-based test that generates a risk score (Paik et al., 2003), and the Breast Intergroup is preparing to test this risk score prospectively in a large Phase III trial.

Research on novel biomarkers now offers the possibility of predicting which patients with ER-positive breast cancer will respond to tamoxifen, an important systemic treatment for this type of cancer. One study has shown that pretreatment levels of ER significantly predicted response to tamoxifen treatment; by multivariate analysis, it was associated with 27 times the likelihood of response (Chang et al., 2000). Another study showed that high expression levels of AIb1 (SRC-3), an ER coactivator, in patients not receiving adjuvant tamoxifen therapy was associated with better prognosis and longer disease-free survival, while high AIb1 expression in patients receiving tamoxifen therapy was associated with worse disease-free survival, indicating tamoxifen resistance (Osborne et al., 2003). Thus, AIb1 might be an important diagnostic and therapeutic target.

Continuing Needs and Evolution

Screening film mammography has the best sensitivity and specificity of any existing breast cancer screening tool, but it still needs refinement. In addition, several technologies are being examined for their role in breast cancer detection and diagnosis. For example, researchers are advancing computer-aided diagnostic methods in the hope of improving their reproducibility for consistently accurate diagnosis of breast cancer. Investigations are continuing to assess the utility of MRI for finding small breast lesions that may be missed in mammograms, producing better images of dense or augmented breast tissue, and helping with treatment staging and follow-up. Additional biomarkers are being identified for the various stages of breast cancer development, and research is addressing their potential for risk assessment, screening, and diagnosis. As more and better markers are discovered, it may become possible to develop bioassays that can detect the presence of breast cancer or precancer and predict its clinical course.

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Chapter 7:
Breast Cancer Treatment: NCI's Investment and Recent Progress

The goal of breast cancer treatment research is to dramatically improve management and outcome of all stages of the disease. *Charting the Course: Priorities for Breast Cancer Research*

Research leading to improved cancer treatment plays a prominent role in NCI's cancer portfolio. Treatment research aims to identify and exploit the most promising areas of science and technology to yield important new information that will lead to better therapeutic interventions. It spans activities ranging from discovery of new interventions in the laboratory, to preclinical testing of safety and efficacy in animal models, to phased clinical trials in cancer patients.

In its 1998 report, the Breast Cancer PRG identified several goals for treatment research that, if met, would dramatically improve the management and outcome of all stages of breast disease. These goals included increasing disease-free and overall survival, improving patient outcomes, lowering the incidence of secondary breast cancers, and improving access to the highest-quality medical care for all Americans. The PRG recognized that achieving these endpoints would require improvement in several areas and outlined five priorities in breast cancer treatment research that could guide this effort. For both localized and advanced breast cancer, the PRG stressed the importance of:

- Developing innovative biological approaches for the treatment of breast cancer
- Developing the expertise required for modern clinical investigation
- Facilitating the design and conduct of large-scale clinical trials
- Learning more about breast cancer biology to better predict the clinical course of disease and response to therapy
- Increasing public access to information regarding treatment options and clinical trials

The NCI has been responsive to these PRG priorities. In the years since the release of the PRG report, the NCI has supported a wide range of research projects, training programs, and clinical trials that address these treatment-related priorities. As a result, there has been an increase in the number of effective therapeutic drugs in clinical practice, the number of ongoing breast cancer clinical trials testing new agents, and the rate of patient accrual to these clinical trials. One of the most notable advancements over the past 5 years in breast cancer treatment has been the shift in focus from using high-dose systemic chemotherapy regimens to the development of targeted therapies that are more effective and less toxic. The field of targeted therapeutics was pioneered by the monoclonal antibody-based drug, trastuzumab (Herceptin®), which was approved in 1998 for treatment of Her2-overexpressing metastatic breast cancer. In the ensuing years, several other classes of novel anticancer drugs and targeted delivery systems, including aromatase inhibitors and immunoliposomal vehicles, have been developed and are currently undergoing preclinical and clinical testing. In 1999, the aromatase inhibitor exemestane (Aromasin®) was approved for the treatment of breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy, making it the fourth aromatase inhibitor approved by the U.S. Food and Drug Administration (FDA) for the treatment of breast cancer.

Since the release of the 1998 PRG report, NCI has sponsored a major report that is relevant to recommendations of the Breast Cancer PRG for treatment. The report, *National Institutes of Health Consensus Development Conference Statement: Adjuvant Therapy for Breast Cancer, November 1–3, 2000*,[1] summarizes currently available data on the use of adjuvant therapy for breast cancer. A 14-member panel developed conclusions based on evidence presented by experts in medical oncology, radiation oncology, biostatistics, epidemiology, surgical oncology, and clinical trials. The panel concluded that women should only receive adjuvant hormonal therapy if their tumors express hormone-receptor protein. Most women with localized breast cancer should receive adjuvant polychemotherapy, regardless of lymph node, menopausal, or hormone-receptor status, because it

1 Published in the Journal of the National Cancer Institute. 2001 Jul 4;93(13):979-89.

improves survival. The panel also pointed to the critical need for trials to evaluate the role of adjuvant chemotherapy in women older than 70 years and the impact of its side effects on quality of life.

NCI's Investment and Response

From FY1998 to 2003, the NCI's extramural investment in research on breast cancer treatment has increased from $52.0 million to $108.2 million (Figure 7-1). This increase in funding corresponds to increases in the number of projects that are responsive to PRG priorities in treatment research.

Table 7-1 summarizes the NCI's responsiveness to the five Breast Cancer PRG research priorities for treatment. In addition, NCI's responsiveness to one of the original PRG priorities on breast cancer genetics is summarized in Table 7-1.[2]

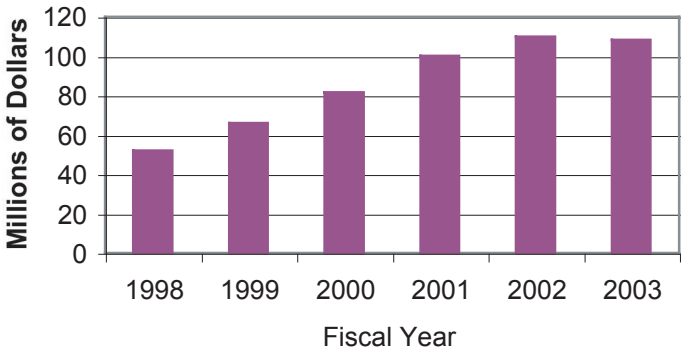
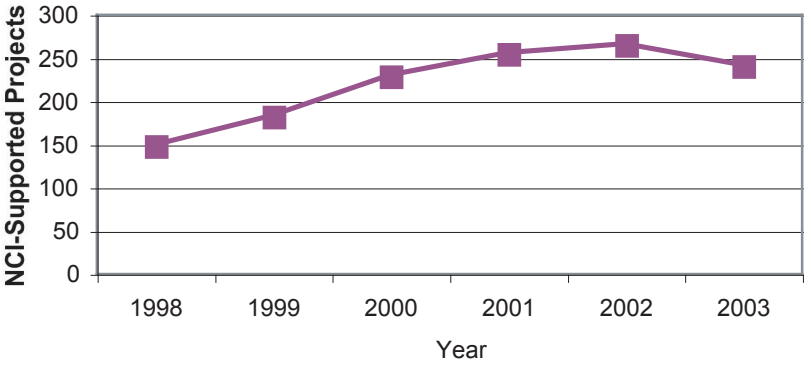


Figure 7-1. NCI's extramural investment in breast cancer treatment research: 1998-2003 (in millions of dollars)

Table 7-1. NCI Efforts Responsive to PRG Priorities and Opportunities in Treatment

PRG Priority:

How can we develop innovative biological approaches to the treatment of breast cancer, in the laboratory and via small (pilot) trials?



NCI Efforts:

- In FY2003, examples of active areas of investigation included the association of a novel gene (*wth3*) with multidrug resistance; specific immunotherapy with monoclonal antibodies; novel cytotoxic products derived from marine sponges; biosynthesis of maytansinoids and analogs; drug discovery by mirror image ligand display; combinatorial creation of new anticancer agents; synthesis of WS9885B, a novel cytotoxic tubulin binder; novel therapeutic uses of phenylacetate in breast cancer; stress-induced bystander effects in cancer treatment; and preclinical evaluation of a novel apoptosis-inducing antitumor agent (MX2060).
- Examples of clinical trials addressing this priority included the following:
  - Phase I Pilot Study of Her2/*neu* Intracellular Domain Protein-Pulsed Autologous Dendritic Cells in Patients With Her2/*neu* Expressing Advanced Malignancies Showing No Evidence of Disease After Standard Treatment (DUMC-1309-00-7R1
  - Phase I Study of LMB-9 Immunotoxin in Patients With Advanced Colon, Breast, Non-Small Cell Lung, Bladder, Pancreas, or Ovarian Cancer (MSGCC-9981)
  - Phase I/II Randomized Study of Monoclonal Antibody CAL Versus Zoledronate in Women With Breast Cancer and Bone Metastases (CWRU-080235)

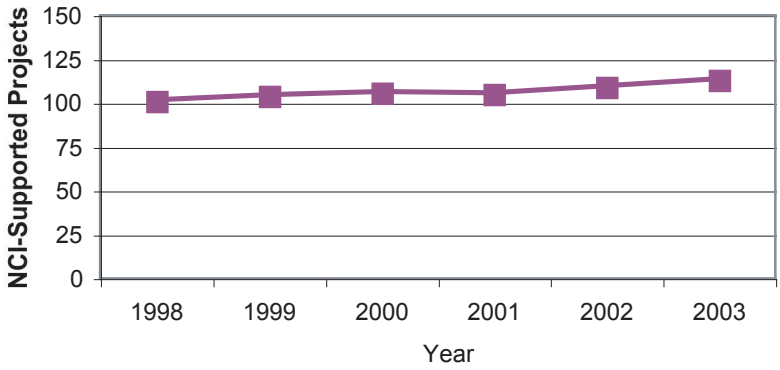
2 A project may map to more than one PRG priority and therefore be represented in more than one figure. Projects active in 2003 are listed in Appendix B (Tables B-33 to B-39) by Principal Investigator's name for each PRG priority.

- Pilot Phase II study of sequential PANVAC-VF followed by the addition of docetaxel in metastatic breast cancer (LOI 6977 approved)
- Pilot Study to Evaluate Angiogenesis After Treatment With Bevacizumab (Anti-VEGF Humanized Monoclonal Antibody) in Previously Untreated Patients With Inflammatory Breast Cancer or Locally Advanced Breast Cancer (01-C-0173)
- Phase II Randomized Study of Anastrozole and Gefitinib Versus Fulvestrant and Gefitinib in Postmenopausal Women With Recurrent or Metastatic Hormone Receptor-Positive Breast Cancer (ECOG-4101)
- Phase Ib/II Neoadjuvant Study of Tipifarnib, Docetaxel, and Capecitabine in Patients With Locally Advanced or Metastatic Solid Tumors or Stage IIIA or IIIB Breast Cancer (NCI-5599)

- On September 28-29, 1999, NCI sponsored the first biannual *National Cancer Institute-Cancer Therapy Evaluation Program (CTEP) Drug Development Meeting*. On January 31-February 1, 2001, NCI Sponsored the *Workshop on Potential Clinical Applications for GnRH Antagonists*. On October 5–6, 2000, NCI sponsored a meeting on *Novel Molecular Targets for Cancer Therapy*.
- NCI initiatives addressing this priority included the Specialized Program of Research Excellence (SPORE) in Breast Cancer, Cancer Drug Discovery: Diversity Generation and Smart Assays, Cancer Therapy-Related Use of Genetically Engineered Mice, Clinical Proteomics Program (CPP), Exploratory Grants for Correlative Laboratory Studies and Clinical Trials, Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses (FLAIR), Molecular Target Drug Discovery for Cancer, National Cooperative Drug Discovery Groups (NCDDGs), Quick Trials for Novel Cancer Therapies, Rapid Access to Intervention Development (RAID) Program, Rapid Access to NCI Discovery Resources (RAND), Therapeutic Modulation of Angiogenesis in Disease, and Unconventional Innovations Program (UIP).

PRG Priority:

How can we facilitate the design and conduct of large clinical trials in breast cancer, focusing on the endpoints of longer disease-free and overall survival, reduced treatment toxicity, reduced breast cancer incidence, and ease of delivery to the entire population (including rural patients, the elderly, the economically disadvantaged, and members of minority groups)?



NCI Efforts:

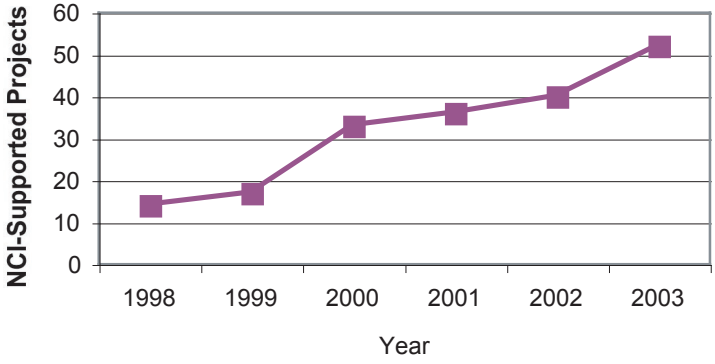
- In FY2003, examples of active areas of investigation included enhancing Native American participation in radiotherapy trials, understanding barriers to enrolling the elderly in cancer trials, evaluating cancer disparities among Hispanic communities, adjuvant hormonal therapy for Vietnamese women with breast cancer, simultaneous thermo-radiotherapy for breast carcinoma, and numerous trials conducted at clinical oncology program centers.
- Examples of clinical trials addressing this priority included the following:
  - Correlation of Menstrual Cycle Phase at the Time of Surgery With Disease-Free Survival in Premenopausal Women With Stage I or II Breast Cancer (NCCTG-N9431)
  - Phase III Randomized Study of Paclitaxel via One-Hour Infusion Every Week Versus 3-Hour Infusion Every 3 Weeks With or Without Trastuzumab (Herceptin®) in Women With Inoperable, Recurrent, or Metastatic Breast Cancer With or Without Overexpression of Her2/*neu* (CLB-9840)

- Phase III Prognostic Study of Sentinel Node and Bone Marrow Micrometastases in Women With Stage I or IIA Breast Cancer (ACOSOG-Z0010)
- Phase III Randomized Study of Neoadjuvant Docetaxel and Carboplatin With Versus Without Trastuzumab (Herceptin®) in Women With Locally Advanced Breast Cancer (UCLA-9911084)
- Phase III Randomized Study of Four Schedules of Adjuvant Doxorubicin, Cyclophosphamide, and Paclitaxel in Patients With Node-Positive or High-Risk Node-Negative Breast Cancer (SWOG-S0221)
- Phase III Randomized Study of Letrozole Versus Placebo in Postmenopausal Women With Primary Breast Cancer Who Have Completed at Least Five Years of Adjuvant Tamoxifen (MA.17)
- Phase III Randomized Study of Sequential Chemotherapy Using Doxorubicin, Paclitaxel, and Cyclophosphamide or Concurrent Doxorubicin and Cyclophosphamide Followed by Paclitaxel at 14 and 21 Day Intervals in Women With Node-Positive Stage II or IIIA Breast Cancer (CALGB-9741).

- NCI initiatives addressing this priority included the Cancer Trials Support Unit (CTSU), Clinical Trials Cooperative Group Program, Community Clinical Oncology Program (CCOP), Cooperative Planning Grant for Cancer Disparities Research Partnership, Expanded Participation Project (EPP), and Minority-Based Community Clinical Oncology Program (MBCCOP).

PRG Priority:

How can we develop the expertise required for modern clinical investigation?

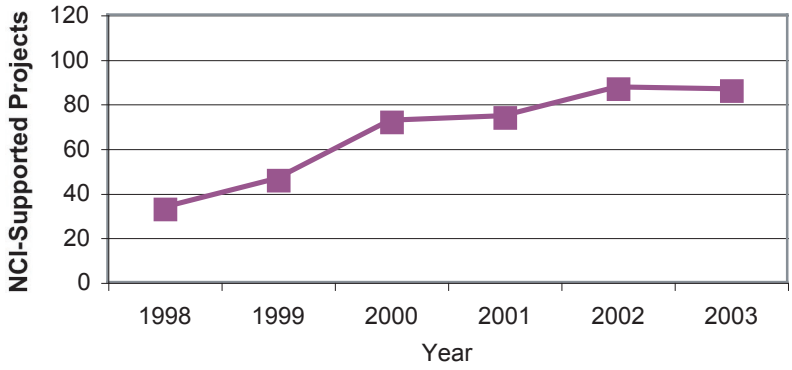


NCI Efforts:

- In FY2003, examples of active areas of investigation included a physician-scientist training program for clinical investigation protocol development, role of Her4 as a differentiation factor in breast cancer, clinical research in stem cell transplantation, education and training of surgical oncologists in the biologic basis of cancer and translational research, continued funding for a quality assurance review center, training physician-scientists to develop specific targets for therapy based on genetic and epigenetic alterations in cancer cells, semi-parametric and empirical process methods in oncology, urban Latino and African-American cancer disparities project, and a workshop on the nuclear radiology of breast cancer.
- On November 1-3, 2000, NCI sponsored the *Adjuvant Therapy for Breast Cancer-National Institutes of Health (NIH) Consensus Development Conference*. On April 26-28, 2000, NCI sponsored the *NIH Selective Estrogen Receptor Modulators (SERMs) Workshop*. On October 5-6, 2000, NCI sponsored *Novel Molecular Targets for Cancer Therapy*.
- The Center for Cancer Research at NCI provides training programs for postdoctoral fellows that focus on translational research projects in clinical oncology, cultural sensitivity training, and scientific management training.
- The recently introduced cancer Biomedical Informatics Grid (caBIG) is addressing some of these issues by assembling basic and clinical informatics tools that can be used widely by the cancer research community. In addition, caBIG is supporting the development of new tools by biomedical researchers.
- NCI initiatives addressing this priority included Breast SPOREs; Cancer Research Training, Career Development and Education Opportunities; Shared Resources for Scientists Outside NCI Cancer Centers; Special Populations Networks (SPNs); and Translational Research Initiative (TRI).

PRG Priority:

How can we learn more about the biology of breast cancer for the purpose of predicting clinical course and predicting response to therapy?

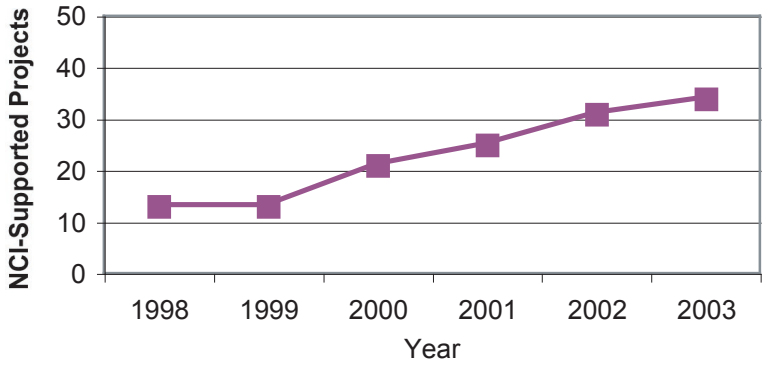


NCI Efforts:

- In FY2003, examples of active areas of investigation included evaluation of biologic endpoints and pharmacokinetics in patients with metastatic breast cancer after treatment with erlotinib, protein kinase C as a marker in tamoxifen-resistant breast cancer, defective estrogen receptors in breast tumors, the role of proteinase-3 in apoptosis and drug resistance, identification of paclitaxel-resistance genes, understanding how glutathione-s-transferase (GST) synergizes with the MRP toxin efflux transporter in multidrug resistance, and genetic modulation of cellular radiation responses.
- On December 4-5, 2003, NCI sponsored the *Linking Haplotypes and Genetic Variation With Cancer Risk Assessment, Prevention, Detection, and Treatment Workshop*.
- Clinical trials and related programs addressing this priority include:
  - Phase II Pilot Study of cDNA Microarray as a Measure of Tumor Response to Neoadjuvant Docetaxel and Capecitabine Followed by Surgery and Adjuvant Doxorubicin and Cyclophosphamide in Patients With Stage II or III Breast Cancer (NCI-00-C-0149)
  - Program for the Assessment of Clinical Cancer Tests (PACCT)
- NCI initiatives addressing this priority included the Cancer Molecular Analysis Project (CMAP), Cancer Prognosis and Prediction, and the Cooperative Human Tissue Network (CHTN).

PRG Priority:

Access to accurate information on treatment options, including available clinical trials, is critical for patients, their families, and providers.



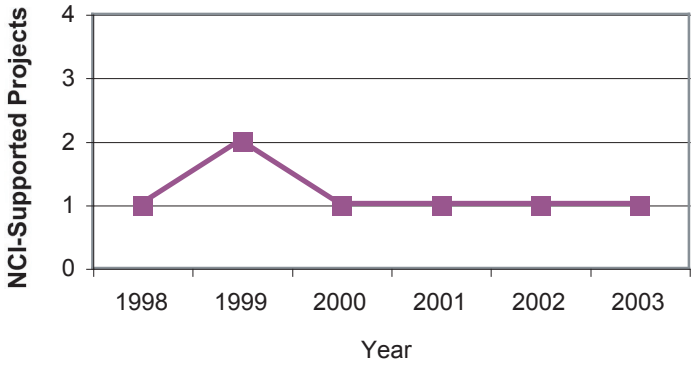
NCI Efforts:

- In FY2003, examples of active areas of investigation included the Urban Latino African-American Cancer Disparities Project, education and collaboration to enhance breast cancer care, the Partnership to Increase Hispanic Cancer Research Education, breast cancer patients' treatment preferences, enhancing Native American participation in radiotherapy trials, training minority scientists in research, overcoming barriers to early-phase clinical trials, educational and outreach approaches for cancer prevention, and improving cancer outcomes for African Americans.
- On August 27-29, 2003, NCI cosponsored the Trans-HHS Cancer Health Disparities Progress Review Group Roundtable.
- NCI resources that provide information about various types of cancer treatment options, including available clinical trials, include the Cancer Information Service (CIS), the NCI Publications Locator, and caMATCH, a computerized system for matching breast cancer patients with trials.

- NCI initiatives addressing this priority included the cancer Biomedical Informatics Grid (caBIG), Community Clinical Oncology Program (CCOP), Expanded Participation Project (EPP), Minority-Based Community Clinical Oncology Program (MBCCOP), Special Populations Networks (SPNs), and the Cancer Trials Support Unit.

PRG Priority:

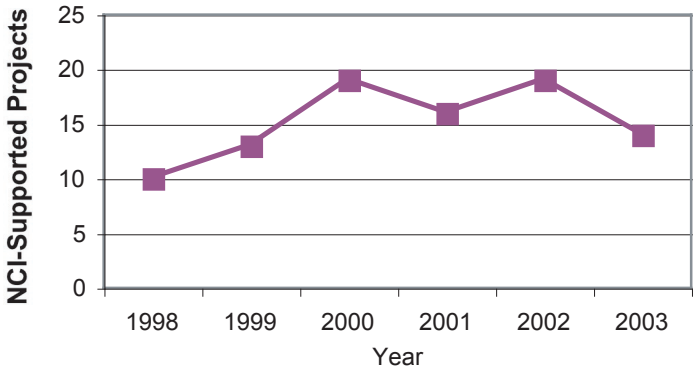
Are different recommendations for extent of surgery or reconstruction appropriate for women with an inherited predisposition?[a]



NCI Efforts:

- In FY2003, an active area of investigation was the national prospective study of risk-reducing salpingo-oophorectomy and ovarian screening among women at increased genetic risk of breast and ovarian cancer.
- NCI-funded researchers participate in the Prevention and Observation of Surgical End Points (PROSE) study group, an international clinical outcomes collaboration addressing the effectiveness of surgery on women with inherited predisposition to breast cancer.
- NCI initiatives addressing this priority included the Cancer Genetics Network (CGN) and Cancer Genetics Services Directory.

Additional Breast Cancer Treatment Projects



NCI Efforts:

- In FY2003, examples of active areas of investigation included percutaneous removal and margin ablation for breast cancer; induction of cell cycle arrest by clotrimazole—an inhibitor of RNA translation initiation; the role of the acetyltransferase *p300* in cellular responses; *p21* transcriptional inhibitors as proapoptotic compounds; healing touch, immunity, and fatigue in breast cancer; *grp78* and hypersensitivity to DNA cross-linking agents; and interleukin-10 for breast cancer therapy.
- Clinical trials and related programs addressing this priority include:
  - Phase II Randomized Study of Metronomic Low-Dose Cyclophosphamide and Methotrexate With or Without Bevacizumab in Women With Metastatic Breast Cancer (DFCI-03083).
- Research in the emerging area of image-guided therapies included magnetic resonance (MR) methods for guiding thermal therapy, anatomic and biologic staging of breast disease with MRI, integrated ultrasonic systems for noninvasive therapy, and MR-guided surgery and radiation therapy.

a. This priority was part of the Genetics section in the original Breast Cancer PRG report.

Clinical trials comprised a large part of the NCI's responsiveness to PRG priorities related to breast cancer treatment. A search of the Physician's Data Query Clinical Trials database for NCI-sponsored breast cancer treatment protocols identified nearly 300 clinical trials that were active between 1998 and 2003.[3] More than 130 of these trials were Phase I or Phase II investigations of innovative biological approaches for breast cancer treatment, and another 55 were large-scale clinical trials.

The initiatives that impacted breast cancer treatment research between 1998 and 2003 include the following list of general initiatives that are described in Table 2-1,[4] as well as the category-specific initiatives described in Table 7-2.[5]

- Aging Women and Breast Cancer
- Applications of Innovative Technologies for the Molecular Analysis of Cancer
- Basic and Preclinical Research on Complementary Alternative Medicine
- Bioengineering Research Grants
- Bioengineering Research Partnerships
- Breast and Ovarian Cancer Family Registries
- Breast Cancer Faculty
- Cancer Biomedical Informatics Grid (caBIG)
- Cancer Centers Program
- Cancer Imaging Program (CIP)
- Cancer Molecular Analysis Project (CMAP)
- Cancer Prognosis and Prediction
- Cancer Research Training, Career Development, and Education Opportunities
- Clinical Trials Cooperative Group Program
- Community Clinical Oncology Program (CCOP)
- Cooperative Breast Cancer Tissue Resource (CBCTR)
- Cooperative Human Tissue Network (CHTN)
- Correlative Studies Using Specimens From Multi-Institutional Treatment Trials
- Developmental/Pilot Projects in Cancer Complementary and Alternative Medicine
- Exploratory Grants for Correlative Laboratory Studies and Clinical Trials
- Flexible System to Advance Innovative Research for Cancer Drug Discovery by Small Businesses (FLAIR)
- Insight Awards to Stamp Out Breast Cancer
- Integrating Aging and Cancer Research
- Interdisciplinary Research Teams for Molecular Target Assessment
- *In Vivo* Cellular and Molecular Imaging Centers (ICMICs)

3 An NCI-sponsored clinical trial in the Physician Data Query (PDQ) database meets one or more of the following criteria: the protocol (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. Information on ongoing treatment trials for the different stages of breast cancer can be obtained via the NCI's Clinical Trials Web page. To limit a search to only those trials that are sponsored by the NCI, it is necessary to use the advanced search function.

4 Initiatives that impact multiple categories of breast cancer research.

5 Initiatives that are unique to the treatment chapter.

- Minority Institution/Cancer Center Partnership (MI/CCP)
- Minority-Based Community Clinical Oncology Program (MBCCOP)
- Molecular Target Drug Discovery for Cancer
- NCI Center for Bioinformatics (NCICB)
- Nonmammalian Organisms as Models for Anticancer Drug Discovery
- Program for the Assessment of Clinical Cancer Tests (PACCT)
- Shared Pathology Informatics Network (SPIN)
- Shared Resources for Scientists Outside NCI Cancer Centers
- Small-Animal Imaging Resource Program (SAIRP)
- Small Grants Program in Cancer Epidemiology
- Special Populations Networks (SPNs)
- Specialized Programs of Research Excellence (SPOREs) in Breast Cancer
- Specimen Resource Locator
- Therapeutic Modulation of Angiogenesis in Disease
- Unconventional Innovations Program (UIP)

Table 7-2. NCI Initiatives Relevant to Breast Cancer Research: Treatment[a]

Initiatives With Breast Cancer-Relevant Components

- Cancer Drug Discovery: Diversity Generation and Smart Assays (RFA-CA-98-009)
  - Overview: Supports multidisciplinary teams of chemists and biologists who propose novel approaches to discover classes of compounds with potential anticancer activity.
  - Relevant Projects Resulting From This RFA: Between 1998 and 2003, two projects relevant to breast cancer research were supported through this RFA. Specific projects can be found in Appendix B, Table B33, by searching for the current RFA number and the previously issued RFA number (RFA-97-006).
- Cancer Therapy-Related Use of Genetically Engineered Mice (PAR-02-051)
  - Overview: Supports the use of genetically engineered mouse models for cancer therapy-related goals.
  - Relevant Research Projects Resulting From This PA: Between 1998 and 2003, one project relevant to breast cancer research was supported through this PA:

    Transgenic Mice as Models for Antivascular Therapy
- Cancer Trials Support Unit (CTSU) (http://www.ctsu.org)
  - Overview: Supports a national network of physicians to participate in NCI-sponsored Phase III clinical trials. Cooperative Clinical Trials Group sites within the United States and Canada are eligible for participation in the CTSU. In addition, the CTSU is now open to physicians and institutions in the United States that are not affiliated with a Cooperative Group.

a Lists of the projects derived from initiatives can be found on the online Supplement to the Breast Cancer Progress Report: Initiative Database.

- Relevant Clinical Protocols Resulting From This Initiative: Current CTSU-listed protocols for breast cancer include:

  Phase III Randomized Study of Axillary Lymph Node Dissection in Women With Stage I or IIA Breast Cancer Who Have a Positive Sentinel Node (ACOSOG-Z0011)

  Phase III Randomized Study of Adjuvant Cyclophosphamide and Doxorubicin Versus Paclitaxel in Women With Node-Negative Breast Cancer (CALGB-40101)

  Phase III Randomized Trial of Adjuvant Chemotherapy Comprising Standard Cyclophosphamide, Methotrexate, and Fluorouracil (CMF) or Doxorubicin and Cyclophosphamide (AC) Versus Oral Capecitabine in Elderly Women With Operable Adenocarcinoma of the Breast (CALGB-49907)

  Phase III Randomized Study of Paclitaxel With or Without Bevacizumab in Patients With Locally Recurrent or Metastatic Breast Cancer (ECOG-2100)

  Phase III Randomized Study of Ovarian Function Suppression in Combination With Tamoxifen Versus Ovarian Function Suppression in Combination With Exemestane Versus Tamoxifen Alone in Premenopausal Women With Endocrine-Responsive Breast Cancer (IBCSG-24-02)

  Phase III Randomized Study of Triptorelin and Exemestane Versus Triptorelin and Tamoxifen in Premenopausal Women With Endocrine-Responsive Breast Cancer (IBCSG-25-02)

  Phase III Randomized Study of Ovarian-Function Suppression and Tamoxifen or Exemestane With Versus Without Adjuvant Chemotherapy in Premenopausal Women With Endocrine-Responsive Resected Breast Cancer (IBCSG-26-02)

  Phase III Randomized Study of Adjuvant Breast Radiotherapy With or Without Regional Radiotherapy in Women With Previously Resected, Early-Stage Invasive Breast Cancer (CAN-NCIC-MA20)

  Phase III Randomized Study of Adjuvant Cyclophosphamide, Epirubicin, and Fluorouracil Versus Cyclophosphamide, Epirubicin, Filgrastim (G-CSF), and Epoetin Alfa Followed by Paclitaxel Versus Cyclophosphamide and Doxorubicin Followed by Paclitaxel in Premenopausal or Early Postmenopausal Women With Previously Resected Node-Positive or High-Risk Node-Negative Stage I-IIIB Breast Cancer (CAN-NCIC-MA21)

  Phase III Randomized Adjuvant Study of Exemestane Versus Anastrozole With or Without Celecoxib in Postmenopausal Women With Receptor-Positive Primary Breast Cancer (CAN-NCIC-MA27)

  Phase III Randomized Study of Adjuvant Doxorubicin and Cyclophosphamide Followed by Docetaxel Versus Doxorubicin and Docetaxel Versus Doxorubicin, Docetaxel, and Cyclophosphamide in Women With Breast Cancer and Positive Axillary Lymph Nodes (NSABP-B-30)

  Phase III Randomized Study of Adjuvant Clodronate With or Without Systemic Chemotherapy and/or Tamoxifen in Women With Early-Stage Breast Cancer (NSABP-B-34)

  Phase III Randomized Study of Anastrozole Versus Tamoxifen in Postmenopausal Women With Ductal Carcinoma *In Situ* of the Breast Undergoing Lumpectomy and Radiotherapy (NSABP-B-35)

  Phase III Randomized Study of Whole-Breast Radiotherapy Versus Observation With or Without Optional Tamoxifen in Women With Good-Risk Ductal Carcinoma *In Situ* of the Breast (RTOG-9804)

  Phase III Randomized Study of Standard Neoadjuvant Doxorubicin and Cyclophosphamide Followed by Weekly Paclitaxel Versus Weekly Doxorubicin and Daily Oral Cyclophosphamide With Filgrastim (G-CSF) Followed by Weekly Paclitaxel in Women With Inflammatory or Locally Advanced Breast Cancer (SWOG-S0012)

Phase III Randomized Study of Four Schedules of Adjuvant Doxorubicin, Cyclophosphamide, and Paclitaxel in Patients With Node-Positive or High-Risk Node-Negative Breast Cancer (SWOG-S0221)

- Central Institutional Review Board (CIRB) (http://www.ncicirb.org/)
  - Overview: Supports an innovative approach to human subjects protection through a "facilitated review" process that can streamline local Institutional Review Board (IRB) reviews of national multicenter cancer treatment trials. A pilot project is currently sponsored by the NCI in consultation with the Department of Health and Human Services Office of Human Research Protections.
  - Relevant Results From This PA: Ten Cooperative Group-sponsored treatment protocols relevant to breast cancer have been approved by the CIRB since its inception in 2001.
- Clinical Cancer Therapy Research (PA-02-002)
  - Overview: Supports the translation of clinical cancer research insights and the development of new agents into innovative cancer therapeutic studies.
  - Relevant Projects Resulting From This PA: Between 1998 and 2003, four projects relevant to breast cancer research were supported through this PA. Specific projects can be found in Appendix B, Tables B6 and B33, by searching for the current PA number and the previously issued PA numbers (PA-99-046 and PA-92-069).
- Cooperative Planning Grant for Cancer Disparities Research Partnership (RFA-CA-03-018)
  - Overview: Supports the planning, development, and conduct of radiation oncology clinical research trials in institutions that care for a disproportionate number of medically underserved, low-income, ethnic, and minority populations but have not been traditionally involved in NCI-sponsored research.
  - Relevant Projects Resulting From This RFA: Between 1998 and 2003, five projects relevant to breast cancer research were supported through this RFA. Specific projects can be found in Appendix B, Tables B34, B35, B37, B45, and B51, by searching for the current RFA number and the previously issued RFA number (RFA-CA-02-002).
- Development and Application of Imaging in Therapeutic Studies (RFA-CA-98-024)
  - Overview: Supports research projects that apply imaging technologies in the assessment of investigational cancer therapeutic agents.
  - Relevant Projects Resulting From This RFA: Between 1998 and 2003, two projects relevant to breast cancer research were supported through this RFA.[b]
- Expanded Participation Project (EPP) (http://spitfire.emmes.com/study/epp)
  - Overview: Supports a demonstration project for providing broader access to Cooperative Group Phase III trials for breast and three other cancer types.
  - Relevant Programs Resulting From This Initiative: Twenty-eight participating institutions have centralized access to data from nine closed Phase III clinical trials on breast cancer.
- National Cooperative Drug Discovery Groups (NCDDGs) (http://dtp.nci.nih.gov/branches/gcob/gcob_web3.html)
  - Overview: Supports broad, innovative, multidisciplinary approaches to the discovery of new synthetic or natural source-derived anticancer drugs.
  - Relevant Projects Resulting From This Initiative: Between 1998 and 2003, six projects relevant to breast cancer research were supported through this PA. Specific projects can be found in Appendix B, Table B33, by searching for the RFA numbers RFA-CA-99-010, RFA-CA-95-020, and RFA-CA-94-007.

b Lists of the projects derived from initiatives can be found on the online Supplement to the Breast Cancer Progress Report: Initiative Database.

- Quick Trials for Novel Cancer Therapies (PAR-03-005)
  - Overview: Supports the rapid development of new therapeutic approaches and the assessment of these agents in pilot, Phase I, and Phase II cancer clinical trials through an accelerated review and funding process.
  - Relevant Research Projects Resulting From This PA: Between 1998 and 2003, 11 projects relevant to breast cancer research were supported through this PA. Specific projects can be found in Appendix B, Tables B24, B26, B33, B36, B39, and B51, by searching for the current PA number and the previously issued PA numbers (PA-00-047 and PA-99-070).
- Rapid Access to Intervention Development (RAID) Program (http://dtp.nci.nih.gov/docs/raid/raid_index.html)
  - Overview: Supports the translation of novel, scientifically meritorious therapeutic interventions from the academic community to the clinic.
  - Relevant Research Projects Resulting From This Initiative: Descriptions of RAID projects that have reached completion are available on the RAID Web site. To date, two breast cancer-relevant projects have been completed:

    A Study of Safety and Immunological Response of Immunotherapy in Patients With Solid Tumors

    Chemo-Immunotherapy for Metastatic Breast Cancer Treatment
- Rapid Access to NCI Discovery Resources (RAND) (http://dtp.nci.nih.gov/docs/rand/rand_index.html)
  - Overview: Supports academic and nonprofit investigators in the discovery of small molecules, biologics, or natural products with the potential for anticancer activity through such mechanisms as the development of high-throughput screening assays, computer modeling, recombinant target protein production and characterization, and chemical library generation.
  - Relevant Project Resulting From This Initiative: One project funded in the latest program cycle is using an MMTV-*neu* mouse model of breast cancer to screen for indoleamine 2,3-dioxygenase (IDO) inhibitors that mediate tumor regression.
- Translational Research Initiative (TRI) (http://ctep.cancer.gov/resources/trf-overview.html)
  - Overview: Supports correlative studies performed during the conduct of sponsored clinical trials of CTEP Investigational New Drug (IND) agents.
  - Relevant Programs Resulting From This Initiative: The TRI supports translational studies using samples from patients who participate in Phase I and Phase II clinical trials. Among the TRI-approved and/or supported protocols, the following are examples of clinical trials open exclusively to breast cancer patients:

    A Phase I Study of GTI-2040 and Capecitabine in the Treatment of Metastatic Breast Cancer

    A Phase Ib/II Neoadjuvant Trial of R115777 With Docetaxel and Capecitabine for Patients With Stage IIIA or IIIB Breast Cancer

    A Phase I-II Study of R115777 (Zarnestra) Plus Doxorubicin and Cyclophosphamide in Patients With Locally Advanced Breast Cancer and Metastatic Breast Cancer (P5598)

    A Phase I Study of Epothilone B Analog (BMS-247550) in Combination With Carboplatin in Recurrent and/or Refractory Solid Tumors

    A Phase II Trial of Primary Therapy With Bevacizumab and Docetaxel for Locally Advanced Breast Cancer

    Phase II Study of Neoadjuvant Doxorubicin, Docetaxel, and Bcl-2 Antisense (Genasense) Therapy for Patients With Locally Advanced Breast Cancer

    Phase II Trial of STI571 in Metastatic Breast Cancer

A Phase II Study of Depsipeptide in Patients With Metastatic Breast Cancer

A Phase II Study of Perifosine in Patients With Metastatic or Advanced Breast Cancer

Vaccination With Breast Cancer/Dendritic Cell Fusions in Conjunction With IL-12

Ongoing NCI Research: Progress in Breast Cancer Treatment

Progress in Preclinical Models

Recent advances in the development of transgenic mouse models displaying aspects of breast cancer disease progression have led to changes in the way promising therapeutic agents are tested. NCI-supported scientists have developed a transgenic mouse model of mammary cancer by expressing recombinant simian virus 40 early-region transforming sequences under the regulatory control of the rat prostatic steroid-binding protein [C3(1)] gene. This strain of mice, termed C3(1)/SV40 Tag, spontaneously develop tumors of the mammary epithelium without hormone supplementation or pregnancy (Maroulakou et al., 1994). Tumor progression in these mice follows a predictable time course and replicates several important stages that occur during human breast cancer progression, including noninvasive carcinoma, invasive carcinoma, and metastasis to bone. These mice provide good preclinical models for testing therapeutic compounds and have been used to demonstrate the effectiveness of several promising agents, including:

- Endostatin, which was shown to delay mammary tumor onset, inhibit the "angiogenic switch," and decrease tumor burden in these mice (Calvo et al., 2002).
- IL-12/pulse IL-2 treatment, which led to complete regression of established mammary carcinoma and prevented neovascularization in developing lesions (Wigginton et al., 2001), and 2-difluoromethylornithine (DFMO) and dehydroepiandrosterone (DHEA) combination, which was shown to inhibit mammary tumor progression in these mice (Green et al., 2001).

In Situ Disease

In situ breast disease—viewed as either noninvasive breast cancer or a precancerous condition—was an uncommon diagnosis until the widespread adoption of screening mammography. In 1998, about 18% of all new breast cancer diagnoses in the United States were identified as ductal carcinoma *in situ* (DCIS). Because a subset of DCIS patients goes on to develop breast cancer in the absence of treatment, the NCI has sponsored research on optimal treatment of *in situ* disease.

Although it was long thought that there was no role for postoperative therapy in the treatment of *in situ* disease, results from the B-24 trial conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP)—an NCI-funded clinical trials cooperative group—revealed that postsurgical tamoxifen is effective at preventing both invasive and noninvasive cancers in the ipsilateral (same) and contralateral (opposite) breasts of women with DCIS who have undergone breast conservation surgery followed by radiation (Fisher et al., 1999). In June 2000, the FDA approved tamoxifen (Nolvodex®)—an antiestrogen compound—as a postsurgical treatment for preventing invasive breast cancer in individuals with DCIS.

The NSABP B-35 trial is currently under way to determine whether postoperative anastrazole—a compound that prevents synthesis of estrogen by inhibiting the enzyme aromatase—is more effective than tamoxifen in preventing subsequent breast cancers in postmenopausal women with DCIS (Phase III Randomized Study of Anastrozole Versus Tamoxifen in Postmenopausal Women with Ductal Carcinoma *In Situ* of the Breast Undergoing Lumpectomy and Radiotherapy).

Operable Disease

Operable breast cancer, encompassing node-negative Stage I and Stage II disease and node-positive Stage II and Stage IIA disease, has traditionally been treated by a multimodal approach that includes surgery with or without subsequent radiation therapy for local control and, when deemed appropriate, postsurgical adjuvant hormonal and/or chemotherapy for systemic

control. NCI-sponsored researchers are attempting to refine all aspects of the traditional treatment paradigm: the specific treatments that are deemed appropriate, the order in which the treatments are administered, the duration and doses at which the treatments are administered, and the specific agents that are administered.

It has long been known that patients with operable node-positive disease are at higher risk for breast cancer recurrence than patients with node-negative disease and that node-negative patients with large tumors are at higher risk than those with small tumors. In the past, adjuvant therapy was not considered necessary for the majority of patients with node-negative breast cancers. The combined results of several NSABP trials have shown that node-negative tumors do benefit from adjuvant treatment (Fisher et al., 2001). In 235 estrogen receptor-negative patients, the 8-year relapse-free survival rate (RFS) was 90% in those who received surgery and adjuvant chemotherapy, compared with 81% in those who received surgery alone. In 1,024 estrogen receptor-positive patients, the 8-year RFS was 95% in those who received standard chemotherapy with tamoxifen, 93% in those who received tamoxifen alone, and 86% in those who received no adjuvant treatment. In another analysis of 1,009 women with tumors less than 1 centimeter in size, it was found that the combination of radiation and tamoxifen was more effective than either radiation or tamoxifen alone in reducing the ipsilateral recurrence rate following lumpectomy (Fisher et al., 2002).

Recently, new diagnostic tests, developed in part from NCI-supported tumor banks in the Cooperative Groups, are refining risk levels for patients with node-negative breast cancer. Women with node-negative breast cancer have an overall survival rate of approximately 70% following surgery alone. Adjuvant chemotherapy can improve the outcome for women destined to relapse. However, our inability to predict relapse has resulted in the overtreatment of a significant percentage of these women. NCI began the PACCT (Program for Assessment of Clinical Cancer Tests), which brought together experts from across the country to assist in the design of a trial to examine prognosis in node-negative tumors. As a result, the NCI-sponsored Cooperative Group, NSABP, in collaboration with an industrial partner (Genomic Health, Inc.), developed the Oncotype DXTM Breast Cancer Assay (Paik, 2003), which provides a recurrence score that correlates very well with 10-year disease-free survival. The PACCT Working Group endorsed the use of the Oncotype DXTM Assay in the trial they are proposing for women with node-negative tumors.

For patients with operable breast cancer, the order in which the various treatment modalities are administered has traditionally been definitive surgery followed by adjuvant chemotherapy (when applicable), followed by radiation (when applicable), and then tamoxifen (when applicable). In the past, preoperative or neoadjuvant therapy was reserved for patients with inoperable breast cancer to render their tumors operable. Recent NCI-sponsored research is defining the role of preoperative systemic therapies in patients with operable disease:

- Preoperative chemotherapy has demonstrated advantages over traditional postoperative adjuvant treatment and provides an opportunity for accelerated drug development. The NSABP B-18 trial demonstrated equivalent outcomes when chemotherapy is given before or after surgical resection of the primary breast tumor (Fisher et al., 1997). However, women with large tumors who had the chemotherapy first were able to undergo breast-conserving surgery more often than their counterparts. In addition, in this trial, the attainment of a pathologic complete remission (PCR) after four cycles of preoperative chemotherapy was strongly predictive of improved outcome. Thus, PCR may serve as a surrogate endpoint, thereby greatly accelerating the evaluation of new drugs and treatment approaches. This concept is being confirmed by the ongoing NSABP B-27 trial, which has completed enrollment and has demonstrated a higher PCR rate when docetaxel (Taxotere®) is given after the combination of doxorubicin (Adriamycin®) and cyclophosphamide (Bear et al., 2003). Disease-free and overall survival results from this trial are awaited to confirm that patients attaining PCR have the best outcome. In the interim, new trials are being designed by two Cooperative Groups to capitalize on this approach:
  - The NCI-supported American College of Surgeons Oncology Group is testing whether preoperative hormonal therapy can produce benefits for postmenopausal women with hormone-sensitive tumors, similar to that seen with preoperative chemotherapy.
  - The NSABP is evaluating new chemotherapy doublets following standard AC chemotherapy in a new preoperative clinical trial.

The trials described above will obtain tumor tissue before and after treatment to assess the genetic profile of the tumor and any changes that occur with therapy. This research should lead to genetic tumor profiles that can predict response to specific chemo-hormonal therapies.

NCI-sponsored clinical trials have continued to refine the doses, administration frequency, and duration of treatments used in patients with operable breast cancer.

- Improvements in radiation therapy may lead to increased utilization of breast-conserving surgery and an improved quality of life. Recent advances in radiation techniques have demonstrated that partial breast irradiation (PBI) given over 5 to 7 days may yield outcomes that are equivalent to the standard 6 weeks of external beam irradiation, which is typically given over the course of 30 visits to a radiation oncology facility (Baglan et al., 2003; Arthur et al., 2003). Two NCI-sponsored Cooperative Groups, NSABP and RTOG, are collaborating on a definitive trial in 3,000 women comparing standard whole-breast irradiation to PBI.
- The NCI-sponsored C9741 trial, performed by The Breast Cancer Intergroup of North America (TBCI), demonstrated that giving the same dose of chemotherapy drugs every 2 weeks instead of the standard every 3 weeks led to improved disease-free and overall survival of women with node-positive breast cancer (Citron et al., 2003). This novel study actually tested two concepts in one trial. The study used standard adjuvant chemotherapy drugs: doxorubin (A), cyclophosphamide (C), and paclitaxel (T). It compared the combination of AC followed by T (AC®T) to the sequential administration of A followed by T and then C (A®T®C) when given either every 2 weeks or every 3 weeks. There was no difference according to whether the drugs were given together or in sequence, but the every-2-week schedule improved both disease-free survival and overall survival at 36 months of median follow-up.
- The ongoing TBCI S0221 trial is determining whether there is benefit to using an even more "dose-dense" regimen. In this trial, the now standard every-2-week AC®T regimen is being compared to daily and weekly administration schedules (Phase III Randomized Study of Four Schedules of Adjuvant Doxorubicin, Cyclophosphamide, and Paclitaxel in Patients With Node-Positive or High-Risk Node-Negative Breast Cancer).

Studies in patients with advanced breast cancer have shown prolonged survival following administration of hormonal therapies that specifically aim to interfere with estrogen stimulation or other tumor growth factors. Recent NCI-sponsored research has been directed at determining whether the therapies that prolong survival in patients with advanced disease are able to decrease the rate of disease recurrence in patients with early breast cancer.

- Aromatase inhibitors (AIs)—compounds that interfere with the synthesis of natural estrogen—were originally used as second-line hormonal therapy in postmenopausal women with estrogen receptor (ER)-positive metastatic breast cancer and later approved for first-line use, in lieu of tamoxifen, in the same patient group. Recent trials have shown that there is benefit to using AIs in adjuvant settings for women with ER-positive, early-stage disease. Ongoing and planned trials are addressing priorities regarding the optimal duration of AI treatment, whether AIs should replace tamoxifen or be used sequentially following completion of tamoxifen therapy, and whether one AI is superior to others with respect to efficacy and toxicity.
- The MA.17 trial, led by the National Cancer Institute of Canada, enrolled over 5,000 women, the majority of whom came from NCI-sponsored U.S. Cooperative Groups (Goss et al., 2003). The trial tested whether disease-free survival is extended by the addition of an AI, letrozole, after 5 years of adjuvant treatment with tamoxifen. Patients who were disease-free after 5 years of tamoxifen therapy were randomized to letrozole or placebo for 5 years. This study was stopped early because significant decrease in recurrence was observed compared with the placebo group. While letrozole seemed to result in a slight increase in osteoporosis, other side effects were generally mild and well tolerated. Further follow-up of long-term toxicity will be important.
- TBCI is leading the current MA.27 trial that directly compares two AIs, anastrozole and exemestane, to compare the event-free survival in postmenopausal women with receptor-positive breast cancer (Phase III Randomized Adjuvant Study of Exemestane Versus Anastrozole With or Without Celecoxib in Postmenopausal Women With Receptor-Positive Primary Breast Cancer).

- In September 1998, trastuzumab (Herceptin®) was approved by the FDA for treatment of metastatic breast cancer. After recognizing the effectiveness of Herceptin® in advanced breast cancer, NCI-supported Cooperative Groups moved quickly to launch two adjuvant trials—N9831 (Phase III Randomized Study of Doxorubicin Plus Cyclophosphamide Followed by Paclitaxel With or Without Trastuzumab [Herceptin] in Women With Her-2-Overexpressing Node-Positive or High-Risk Node-Negative Breast Cancer) and NSABP B-31 (Phase III Randomized Study of Doxorubicin and Cyclophosphamide Followed by Paclitaxel With or Without Trastuzumab [Herceptin] in Women With Node-Positive Breast Cancer That Overexpresses HER2)—to determine whether chemotherapy with Herceptin® is more effective than chemotherapy without Herceptin® in tumors that overexpress Her2/*neu*.
- Bisphosphonates are agents that interfere with bone osteoclasts and are able to disrupt the development of bone metastases from breast tumors. The bisphosphonate pamidronate (Aredia®) is approved in the U.S. for the treatment of advanced metastatic disease. NSABP is performing a definitive trial to test whether the oral bisphosphonate, clodronate, would prevent the development of bone metastases in the adjuvant setting (Phase III Randomized Study of Adjuvant Clodronate With or Without Systemic Chemotherapy and/or Tamoxifen in Women With Early Stage Breast Cancer). In addition, TBCI and NSABP are collaborating on a trial to compare clodronate, zoledronate, and ibandronate to determine whether there is a preferable bisphosphonate for the prevention of breast cancer metastases.

Nonoperable Disease

Nonoperable breast cancer, encompassing Stage IIIB and metastatic Stage IV disease, is treated systemically with first-line chemotherapy and/or hormonal agents. Second-line and subsequent treatments are attempted when first-line treatments are ineffective or when progression occurs in patients who had previously shown full or partial responses.

Although metastatic breast cancer is considered incurable, considerable effort has been directed at identifying treatments that prolong survival while maintaining quality of life. Patients with progressing metastatic breast cancer are generally the first population in which novel approaches and agents are tested for efficacy. Some of the new treatments examined in recent NCI-sponsored research include:

- The angiogenesis inhibitor, bevacizumab (Avastin®), in combination with paclitaxel as first-line treatment (Phase III Randomized Study of Paclitaxel With or Without Bevacizumab in Patients With Locally Recurrent or Metastatic Breast Cancer)
- The combination of fenretinide and tamoxifen (Phase III Randomized Study of Adjuvant Tamoxifen/Fenretinide Versus Tamoxifen/Placebo in Postmenopausal Women With Receptor-Positive Breast Cancer [Zujewski et al, 1999])
- The retinoid alitretinoin in combination with tamoxifen (Lawrence et al., 2001)
- The combination of all-trans retinoic acid and tamoxifen (Budd et al., 1998)
- The cell-cycle kinase inhibitor flavoperidol (Tan and Swain, 2002)
- R11557 (Zarnestra®), an inhibitor of protein farnesylation, in combination with the aromatase inhibitor letrozole (Zujewski et al, 2000)
- ZD1839 (Iressa®), an epidermal growth factor inhibitor, in combination with Herceptin® (Phase II Study of Trastuzumab (Herceptin®) and Gefitinib in Patients With Metastatic Breast Cancer That Overexpresses Her2-*neu*).
- Her2/*neu* vaccines (Disis et al., 2004)
- Anti-MUC-1 monoclonal antibody (Phase I Study of Vaccination Comprising Recombinant Vaccinia-MUC-1 and Recombinant Vaccinia-TRICOM Vaccine in Patients With Metastatic Breast Cancer)
- The apoptosis-inducing drug ceramide for treatment of cutaneous breast cancer (Phase II Study of Topical Ceramide Cream in Women With Cutaneous Breast Cancer).
- Topotecan for advanced breast cancer (Levine et al., 1999)

- Paclitaxel and carboplatin as first-line chemotherapy (Perez et al., 2000).
- The intracellular histamine antagonist N, N-diethyl-2-[4-(phenylmethyl) phenoxy] ethanamine (DPPE) and doxorubicin for patients with anthracycline-naïve metastatic breast cancer (Khoo et al., 1999).

Continuing Needs and Evolution

High priorities for breast cancer treatment research include the development of noninvasive approaches for primary breast cancer ablation and the development of targeted agents that are specific for the various molecular subtypes of breast cancer. Likewise, the discovery of nontoxic agents that block recently understood aspects of the estrogen receptor pathway is critical, as these agents can potentially be used with existing hormonal therapies to improve treatment response rates. Furthermore, efforts to understand patterns of drug sensitivity and resistance would be greatly facilitated by increasing the number of studies that systematically collect tissue samples before and after various therapies.

New areas for development in treatment-based imaging include image-guided applications to enhance intervention efficacy and integrating noninvasive imaging techniques to better appreciate the activity and mechanism of action of targeted therapies in Phase I and II studies. Additionally, newer clinical trial studies may include: (1) large, randomized studies that assign specific treatments based on new molecular parameters; (2) treatment studies in advanced disease based upon the early detection of micrometastases; and (3) smaller adjuvant trials that use pathologic complete response as a definitive endpoint (once this intermediate endpoint is established).

Progress in breast cancer treatment research would be enhanced by the establishment of standards of data collection that facilitate inter-Institute collaboration, data sharing, and leveraging of projects. The recently established cancer Biomedical Informatics Grid (caBIG) is a major development to facilitate these aims through standardization of computing tools, language, and resources for use by the cancer and biomedical research community. In a similar vein, enrollment in breast cancer treatment trials has been steadily improving over the past few years, ever since the establishment of the Cancer Trials Support Unit (CTSU). Breast cancer accounts for over 50% of all enrollments via this new NCI mechanism. The CTSU allows all qualified oncologists access to NCI-sponsored Phase III treatment trials, thereby speeding up the time to answer important questions and enhancing patient access to innovative therapies.

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Chapter 8:
Breast Cancer Control, Survivorship, and Outcomes: NCI's Investment and Recent Progress

To reduce the burden of breast cancer, we must sustain a vigorous and substantial commitment to basic and applied cancer control research conducted by scientists from diverse disciplines. Such an integrated research effort should address monitoring, prevention, surveillance, detection, treatment, and follow-up, including the provision of compassionate palliative care to those who die of the disease.... A fuller understanding is needed as to which groups of women are at risk for poor quality of life and psychosocial outcomes, and at what points along the disease or care continuum risks are elevated. *Charting the Course: Priorities for Breast Cancer Research*

The ultimate goal of cancer control research, as defined by the 1998 Breast Cancer PRG report, is to eliminate the burden of cancer. NCI has made much progress toward this goal, and recent research has shown that early detection and treatment of breast cancer have contributed to reduced mortality. NCI is supporting research to increase the numbers of women screened, enhance screening methodologies, ensure that all women receive needed treatment, and maximize quality of life for the growing numbers of breast cancer survivors. Several Centers of Excellence are developing communication strategies that will inform women about behaviors that can reduce their risk of developing breast cancer, recruit more women for breast cancer screening, enhance women's decision making about screening and treatment, and improve quality of life following breast cancer treatment. The seven research sites of the Breast Cancer Surveillance Consortium (BCSC) are assessing the accuracy, cost, quality, and intermediate outcomes of screening as it is practiced in the community. Data from the Consortium are critical to related NCI efforts (such as the Cancer Intervention and Surveillance Modeling Network [CISNET]) to estimate the impact of these practices on changes in breast cancer mortality. NCI-supported researchers are also addressing quality of life in breast cancer survivors and the impact of breast cancer on family members.

The PRG report identified 8 priorities that deal with important topics in breast cancer control research and 16 priorities that address critical issues in outcomes research. The cancer control priorities address the need to identify the mechanisms responsible for basic behavioral change, determine whether psychosocial factors influence traditional disease outcomes, facilitate better patient decision making, improve the delivery of breast cancer care to maximize desirable outcomes and minimize cost, identify the psychosocial benefits from unproven treatments, use advances in communications technology to study ways of delivering breast cancer information, determine the impact of breast cancer on the family, and identify communications strategies to reach diverse health providers. Outcomes priorities focus on the need to study the short- and long-term outcomes of multimodal treatment for breast cancer, investigate patient-focused outcomes across the continuum of age and for women with *in situ* breast cancer, integrate patient-focused data with biological prognostic information to make treatment decisions, improve patient outcomes, help meet survivors' needs, identify resources to study patient-focused outcomes, improve the management of symptoms and side effects, incorporate patient preferences into treatment decisions, collect patient outcome data in prevention trials, and advance the field of outcomes research.

The NCI has been responsive to the PRG priorities related to breast cancer control, survivorship, and outcomes. Recent research has demonstrated that certain recruitment strategies can increase the numbers of women who are screened for breast cancer at recommended intervals. Several factors have been identified that can improve the accuracy of mammography. As a result of research, treatment following an abnormal mammogram has improved in recent years, and disparities in the care received are being addressed. As more women survive with breast cancer, researchers are identifying the factors—such as social support and exercise—that maximize physical and emotional functioning.

Since the release of the PRG report, NCI has sponsored or cosponsored at least four major reports that are relevant to the Cancer Control, Survivorship, and Outcomes recommendations of the Breast Cancer PRG. In addition, the National Institutes

of Health *Consensus Development Conference Statement: Adjuvant Therapy for Breast Cancer, November 1-3, 2000*, addressed issues related to patient-focused outcomes when making decisions about adjuvant therapy (see Chapter 7 for details).

The first of these reports, *Evaluating Screening Performance in Practice*,[1] was developed by the Breast Cancer Surveillance Consortium. The BCSC is a consortium of seven research sites and one statistical coordinating center established by the NCI to address issues that can be adequately examined only in a very large sample drawn from diverse geographic and practice settings. This report describes the BCSC's current areas of research and its accomplishments to date, including more than 130 papers in peer-reviewed journals. One of the studies highlighted in the BCSC report found that screening mammography was less effective for detecting cancer in younger women than in older women, regardless of family history. This study shows the importance of further research to determine whether screening mammography is accurate enough to support screening recommendations for younger women with a family history of breast cancer. Another study found that mammography was equally accurate in black and white women but that black women with symptoms had larger and more aggressive tumors than white women. These results indicate that more research is needed to clarify the relationship between race/ethnicity, modifiable risk factors, and stage of disease at diagnosis.

The second report, *Exploring the Role of Cancer Centers for Integrating Aging and Cancer Research*,[2] summarizes the deliberations of a workshop organized by the NCI and the National Institute on Aging. The report notes the disproportionately high burden of cancer for older Americans, a particular concern in the context of the aging population in the United States. Workshop participants met in seven breakout sessions focused on such issues as treatment efficacy and tolerance; effects of comorbidity and cancer; and psychological, social, and medical issues. Each group developed three recommendations, including: incorporate the clinical expertise from NCI projects, particularly the NCI SEER projects, that is available in cancer centers to improve the quality of care of the medically underserved, aging population; develop clinical trials that are specifically designed for older cancer patients; develop models for decision making at the individual and clinical levels; and examine the cancer caregivers' functioning and quality of life and their impact on the older cancer patient's care and treatment trajectory. This report resulted in an NCI Program Announcement: Integrating Aging and Cancer Research.

The NCI's 2002 *Report of the Breast Screening Working Group*, prepared at the request of the NCI Director, was developed in response to debates in the professional literature and the news media about mammography's efficacy in certain age groups. This internal report was intended to help the Institute improve how it translates complex research evidence for the public and to examine the state of the science and what research and resources are needed to promote progress in breast cancer screening and diagnosis. The Working Group made several recommendations in its report, including increasing basic research on interval cancers, tumor microenvironment, and ductal carcinoma *in situ* (DCIS), and supporting translational research, technology development, and interdisciplinary collaboration. The Working Group also recommended that NCI communicate proactively and clearly about research on screening mammography to ensure that its key audiences are well informed.

The NCI cosponsored the Institute of Medicine's report *Meeting Psychosocial Needs of Women With Breast Cancer*.[3] This report was intended to examine the psychological consequences of the cancer experience, the availability and application of psychosocial services for women with cancer, and the training and education of cancer care providers. In a review of the literature, the report concludes that psychosocial interventions can be expected to reduce psychiatric symptoms and improve quality of life in routine breast cancer care. The report presents recommendations for providers and the delivery of care through: (1) promoting formal psycho-oncology education for oncology providers; (2) integrating standards of psychosocial care with cancer managemen; and (3) conducting collaborative studies to enhance the integrated coordination of care. The report also recommends to continue studies on psycho-oncology research and to encourage an NCI special study to ascertain the use of, and current need for, cancer-related supportive care services in the United States, including disparities by age, race/ethnicity, geography, and insurance coverage.

1 This report can be found on the BCSC Web site at http://breastscreening.cancer.gov/espp.pdf.

2 Available at http://www.nia.nih.gov/health/nianci/.

3 A brief review of this report can be found on the IOM Web site at http://www.iom.edu/report.asp?id=18136.

NCI's Investment and Response

From FY1998 to 2003, NCI's extramural investment in breast cancer control, survivorship, and outcomes research increased from $46.6 million to $82.8 million (Figure 8-1). This increase in funding corresponds to increases in the number of projects that are responsive to the 24 Breast Cancer PRG research priorities for cancer control, survivorship, and outcomes.

NCI's research support is summarized in Table 8-1 for the 8 Breast Cancer PRG research priorities pertaining to cancer control and in Table 8-2 for the 16 research priorities pertaining to outcomes.[4]

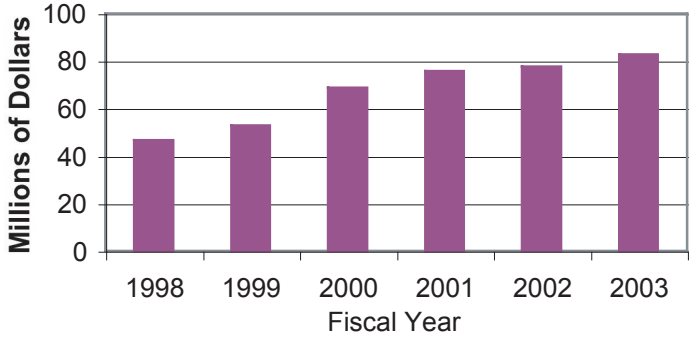
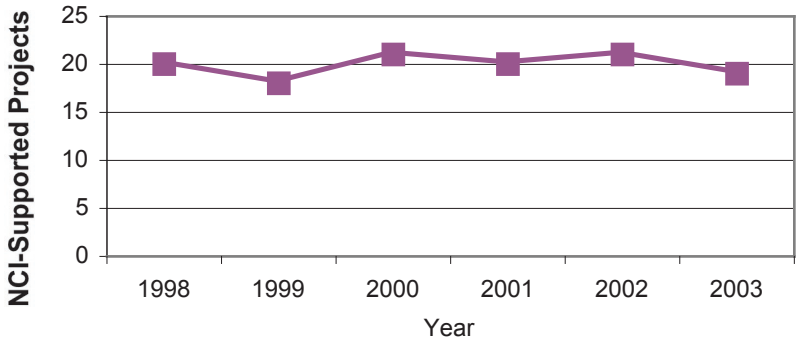


Figure 8-1. NCI's extramural investment in cancer control, survivorship, and outcomes research in breast cancer: 1998-2003 (in millions of dollars)

Table 8-1. NCI Efforts Responsive to PRG Priorities and Opportunities in Cancer Control Research[a]

PRG Priority:

What are the mechanisms responsible for basic behavioral change?



NCI Efforts:

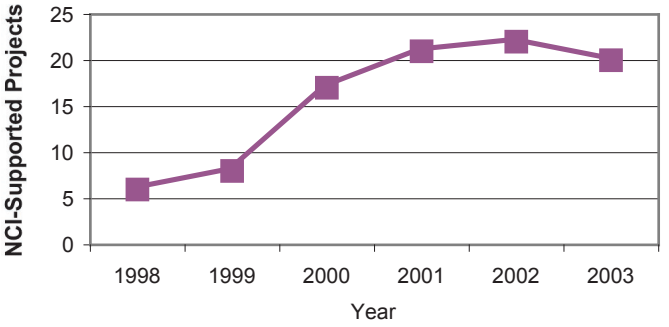
- In FY2003, examples of active areas of investigation included compliance with mammography screening guidelines, with an emphasis on older women, African Americans, and Hispanics; the relationship between trust and breast cancer prevention practices and behaviors in African Americans; the long-term physiological, psychological, social, and religious/spiritual effects of surviving cancer on older adults; and the impact of concerns about mortality on behavioral risk factors for cancer.
- On October 14-16, 1998, NCI sponsored the *5 A Day International Symposium* to address the health benefits of increased fruit and vegetable intake and behavior change interventions in community settings.
- NCI initiatives addressing this priority included the Small Grants Program for Behavioral Research in Cancer Control and Social and Cultural Dimensions of Health.

a. Some of the original PRG priorities are addressed jointly in Table 8-1 because these priorities address partially overlapping issues and they are relevant to many of the same research projects and initiatives.

4 A project may map to more than one PRG priority and, therefore, be represented in more than one figure. Projects active in 2003 are listed in Appendix B (Tables B-40 to B-58) by Principal Investigator's name for each PRG priority.

PRG Priority:

Do psychosocial factors including, but not limited to, interventions influence traditional disease outcomes (e.g., overall survival, disease-free survival, and disease response)?



NCI Efforts:

- In FY2003, examples of active areas of investigation included the motivations to obtain follow-up care of women who had experienced a false-negative mammogram; the relationships between breast cancer treatments and disease-specific and health-related quality of life outcomes; and the impact of environmental toxins, diet, physical activity, and weight gain on breast cancer risk.
- NCI initiatives addressing this priority included the Breast Cancer Specialized Programs of Research Excellence (SPOREs); Economic Studies in Cancer Prevention, Screening and Care; and Integrating Aging and Cancer Research.

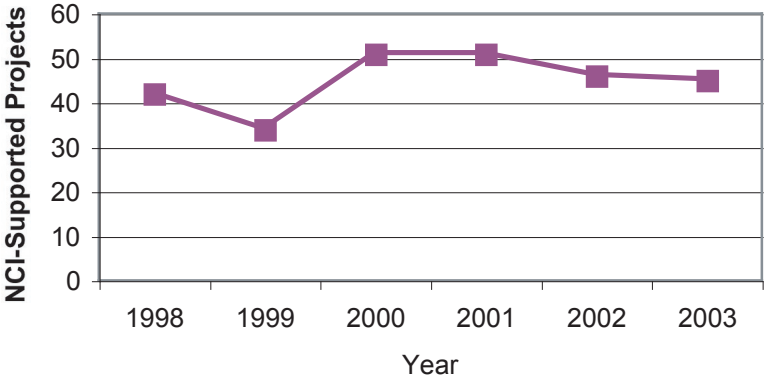
PRG Priorities:

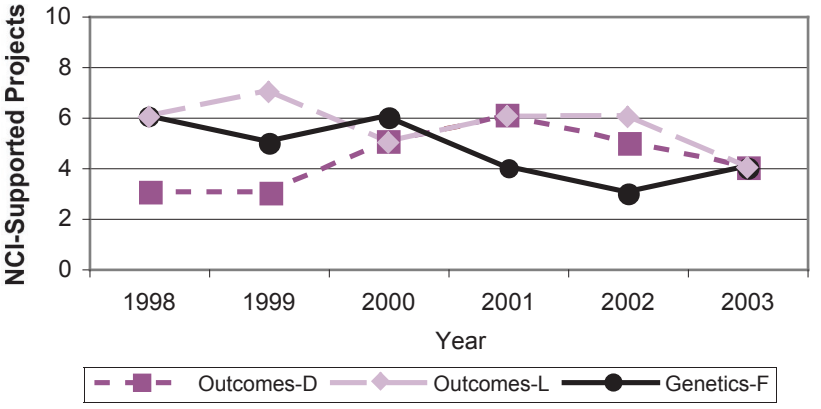
How can we facilitate better patient decision making, especially that based on risks and benefits? (Control-C)

How can patient-focused data be integrated with biological prognostic information to make the best treatment decisions? (Outcomes-D)

How can patient preferences be incorporated into treatment decisions? (Outcomes-L)

Discussion and resolution of social and legal issues of informed consent and privacy of medical information in the context of genetic testing and genetic predisposition.[b] (Genetics-F)





NCI Efforts:

- In FY2003, examples of active areas of investigation relevant to the following priorities included:
  - Control-C: comparative cancer epidemiology, prevention, and control in older minority populations; barriers to the use of symptom-management strategies by patients; the impact of culture, ethnicity, and income on screening behaviors; and the effects of education and counseling on the emotional, physical, and social adjustment of breast cancer patients

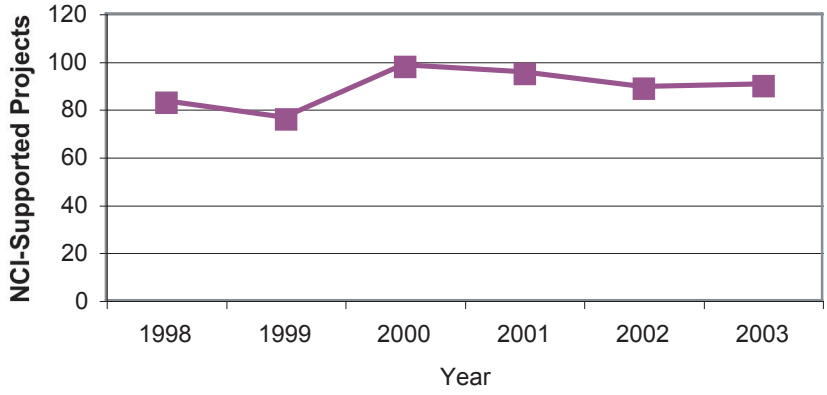
b. This priority was part of the Genetics section in the original Breast Cancer PRG report.

- Outcomes-D: a new functional evaluation tool for assessing cancer care, psychological and immune parameters associated with fatigue in breast cancer survivors, and performance status for decisions about therapies and eligibility for clinical trials
- Outcomes-L: breast cancer patients' preferences for local and systemic therapy
- Genetics-F: decisions about chemoprevention by families with hereditary breast and ovarian cancer and genetic counseling for these families

- Examples of clinical trials addressing these priorities included the following:
  - Randomized Genetics Study of Educational Methods for Patients With Breast or Ovarian Cancer Enrolling in a Breast Cancer Genetics Program (NCI-99-C-0081)
  - Chemotherapy Decisions and Outcomes in Older Women With Newly Diagnosed Breast Cancer (CALGB-369901)
  - Companion Study to Evaluate Quality of Life in Women With Axillary Node-Negative, Estrogen Receptor-Negative, Primary Invasive Breast Cancer Enrolled on Protocol NSABP-B-23 (NSABP-B-23-QOL)
- NCI initiatives addressing these priorities included the Cancer Centers Program, Insight Awards to Stamp Out Breast Cancer, and Special Populations Networks.

PRG Priority:

Can the delivery of breast cancer care from diagnosis and screening through treatment, follow-up, and end of life be improved in ways that maximize desirable outcomes and minimize cost?

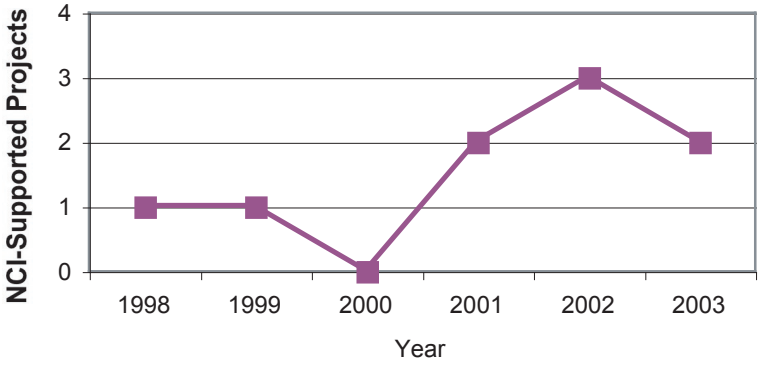


NCI Efforts:

- In FY2003, examples of active areas of investigation included culturally sensitive educational materials to improve screening use in minority populations; the impact of changes in behaviors, clinical practice patterns of health care providers, and interventions on incidence and mortality; effects and costs of a prevention case manager to improve cancer early detection; and a comparison of cancer diagnoses, interventions, and clinical and cost outcomes between persons with and without disabilities.
- Examples of clinical trials addressing this priority included the following:
  - Correlation of Menstrual Cycle Phase at the Time of Surgery With Disease-Free Survival in Premenopausal Women With Stage I or II Breast Cancer (NCCTG-N9431)
  - Randomized Study of Brief Physician-Initiated Smoking Cessation Strategies Versus Usual Care in Patients With Early-Stage Cancer Who Are Undergoing Treatment in Clinical Oncology Settings (NCI-P93-0042)
- NCI initiatives addressing this priority included Aging Women and Breast Cancer, Minority Institution/Cancer Center Partnership (MI/CCP), and Small Grants Program for Behavioral Research in Cancer Control.

PRG Priority:

What psychosocial benefits do patients obtain from unproven treatments that cause them to seek out such treatments?

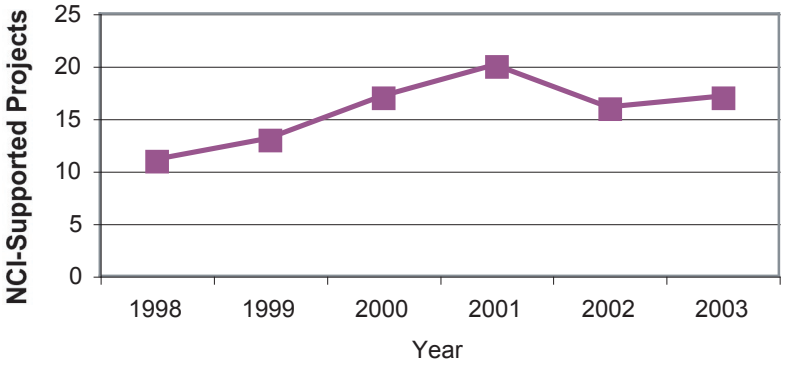


NCI Efforts:

- In FY2003, examples of active areas of investigation included spiritually based health education in African-American women and treating chemotherapy-induced nausea with acupressure.
- Examples of clinical trials addressing this priority included the following:
  - Phase III Randomized Study of Acupressure for Chemotherapy-Induced Nausea in Women With Breast Cancer Receiving One of Three Combination Therapy Regimens (MDA-NUR01-396)
  - Phase III Randomized Study of Black Cohosh for the Management of Hot Flashes in Women With Breast Cancer or Who Have Concerns About Developing Breast Cancer (NCCTG-N01CC)
  - Randomized Study of Acupuncture for Mucositis-Related Pain Secondary to High-Dose Chemotherapy in Patients Undergoing Hematopoietic Stem Cell Transplantation (NCI-03-C-0125)
  - Phase I/II Randomized Study of Adjuvant Doxorubicin and Cyclophosphamide With or Without Chinese Herbal Therapy for Symptom Management in Women With Stage I, II, or Early Stage III Breast Cancer (UCSF-CRO-97755)
  - Study of the Use of Complementary and Alternative Medicine Practices by Women at Increased Risk for Breast Cancer (NCI-00-C-0039)
- On June 9-11, 2000; October 19-21, 2001; and April 9-13, 2003, NCI sponsored *Comprehensive Cancer Care: Integrating Complementary and Alternative Therapies* to provide information on complementary and alternative therapies (CAM) for cancer to oncologists, other practitioners, and people with cancer.
- NCI initiatives addressing this priority included Basic and Preclinical Research on Complementary and Alternative Medicine (CAM) and Centers for Complementary and Alternative Medicine Research.

PRG Priority:

How can advances in communication technologies best be used for research in health communications and behavior change and for delivering breast cancer information?



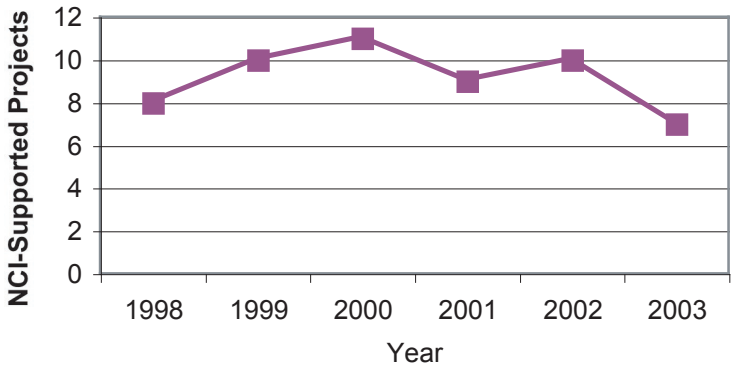
NCI Efforts:

- In FY2003, examples of active areas of investigation included: methods to improve recruitment of patients, especially from minority and low-income populations, into community-based clinical oncology trials; tailored and culturally appropriate communications interventions to increase mammography use; cancer communication among minority populations, including African Americans; and education about risk factors and methods for risk reduction.

- On October 25-28, 2000, NCI sponsored the *11th Annual Conference of the Cancer Patient Education Network (CPEN): Caring, Discovery, Excellence* to exchange information among patient educators from each of the NCI-designated Comprehensive and Clinical Cancer Centers.
- NCI initiatives addressing this priority included the Cancer Centers Program, Centers of Excellence in Cancer Communication Research, and Health Communications in Cancer Control.

PRG Priority:

What is the impact of breast cancer on the family? Specifically, what is its impact on other family members and the family unit, and what is the impact of the family unit on breast cancer outcomes?

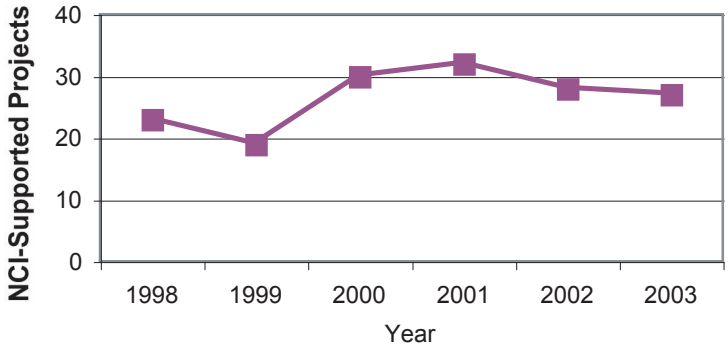


NCI Efforts:

- In FY2003, examples of active areas of investigation included the impact of psychosocial factors on cancer screening behaviors among unmarried women, the effect of education and counseling on patients with breast cancer and their partners, and helping mothers with breast cancer support their children.
- NCI initiatives addressing this priority included the Cancer Outcomes Measurement Working Group (COMWG), Research on the Impact of Cancer on the Family, and Small Grants Program for Behavioral Research in Cancer Control.

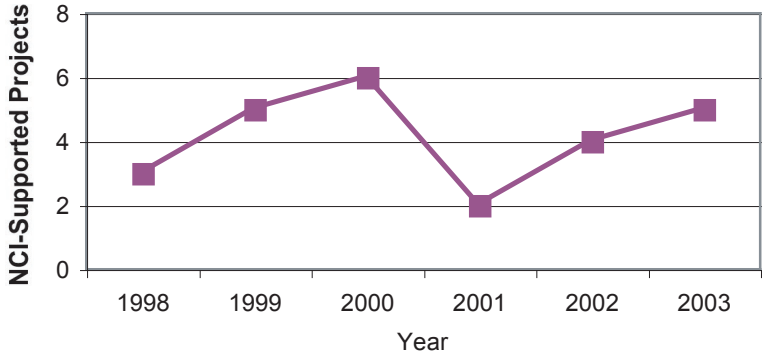
PRG Priority:

What kind of communication strategies are needed to reach the diversity of health care providers in the area of breast cancer?



NCI Efforts:

- In FY2003, examples of active areas of investigation included patterns and outcomes of screening mammography practice in North Carolina and increasing the participation of minority scientists in behavioral and translational cancer research.
- NCI initiatives addressing this priority included Cancer Research Training, Career Development, and Education Opportunities; the MI/CCP; and Special Populations Networks (SPNs).



Additional Breast Cancer Control Projects

NCI Efforts:

- Active research projects in FY2003 related to reducing breast cancer health disparities included: studies of risk-related behaviors and changes in diet and lifestyle in Hispanic breast

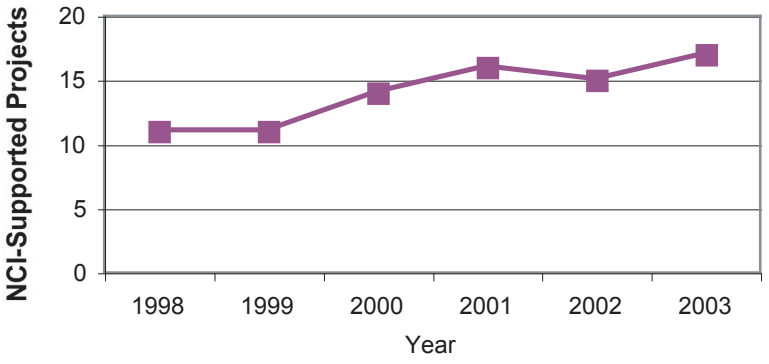
cancer survivors; use of mammograms and/or clinical breast exams and trust in health care providers among black women by level of education, age, income, and Hispanic ethnicity; physician and patient predictors of tamoxifen prescription and treatment adherence in older women; and impact of culture on cancer screening in Chinese women.

- The PRG did not address screening in the context of cancer control, but several areas of investigation on this topic were active in FY2003, including the impact of community factors (such as availability of medical providers) on screening for breast cancer; how low-income African-American women interpret and act on health education messages regarding mammography; effects of soy on estrogen levels and mammographic densities; and the effects of driving distance on mammography use.
- In FY2003, other examples of active areas of investigation included the association between the incidence of breast cancer and body size at different ages, diabetes, and dietary patterns related to insulin resistance and post-treatment behavioral risk factors for recurrence of secondary breast tumors or new primaries.
- Examples of clinical trials addressing screening in the context of cancer control included the following:
  - Screening and Diagnostic Study of Magnetic Resonance Imaging in Women With Suspected Breast Cancer (UPCC-ACR-6884)
  - Randomized Screening and Diagnostic Study of Digital Mammography Versus Screen-Film Mammography in the Detection of Breast Cancer in Women (ACRIN-6652)

Table 8-2. NCI Efforts Responsive to PRG Priorities and Opportunities in Outcomes Research[a]

PRG Priority:

How can patient-focused outcomes be studied across the continuum of age? The impact of breast cancer treatments may be different among different age groups.



NCI Efforts:

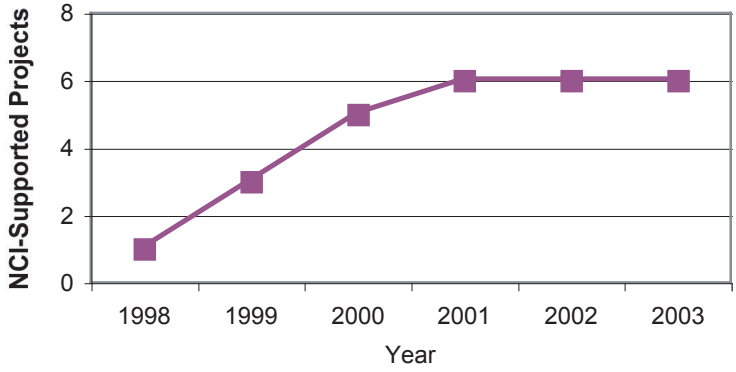
- In FY2003, examples of active areas of investigation included reproductive cancer education resources for women with breast cancer, educating older women about managing uncertainty after breast cancer treatment, helping the mother with breast cancer support her child, and facilitating positive adaptation to a breast cancer diagnosis.
- Examples of clinical trials addressing this priority included the following:
  - Phase II Randomized Study of Soy Protein in Postmenopausal Women With Breast Disease Taking Tamoxifen and Experiencing Hot Flashes (CALGB-79805)
  - Phase III Study of the Effect of Menstrual Cycle Timing With Breast Surgery on Prognosis in Premenopausal Women With Stage I, II, or III Breast Cancer (UCLA-9810046)
  - Phase III Randomized Study of Risedronate for Prevention of Bone Loss in Premenopausal Women Undergoing Chemotherapy for Primary Breast Cancer (NCCTG-N02C1)

a. Some of the original PRG priorities are addressed jointly in Table 8-2 because these priorities address partially overlapping issues and they are relevant to many of the same research projects and initiatives.

- On October 19-20, 2000, NCI sponsored *Cancer Survivorship Throughout the Lifespan: Challenges for the 21st Century* to address the complex medical, psychological, and social needs of cancer survivors.
- NCI initiatives addressing this priority included Integrating Aging and Cancer Research, SEER-Medicare Linked Database, and Small Grants Program for Cancer Epidemiology.

PRG Priority:

What are the patient-focused outcomes for women with *in situ* breast cancer?



NCI Efforts:

- In FY2003, examples of active areas of investigation included assessing quality of life for women with DCIS and studying the effects of various treatment regimens on quality of life for DCIS patients.
- Examples of clinical trials addressing this priority included the following:
  - Screening Study Following Local Excision in Selected Patients With Ductal Carcinoma *In Situ* (DCIS) of the Breast (E-5194)
  - Phase III Randomized Study of Hormone Replacement Therapy for Hot Flashes and/or Vaginal Symptoms in Postmenopausal Women With a History of Node-Negative Invasive Carcinoma or Ductal Carcinoma *In Situ* of the Breast Who Are Receiving Adjuvant Tamoxifen (E-2193)

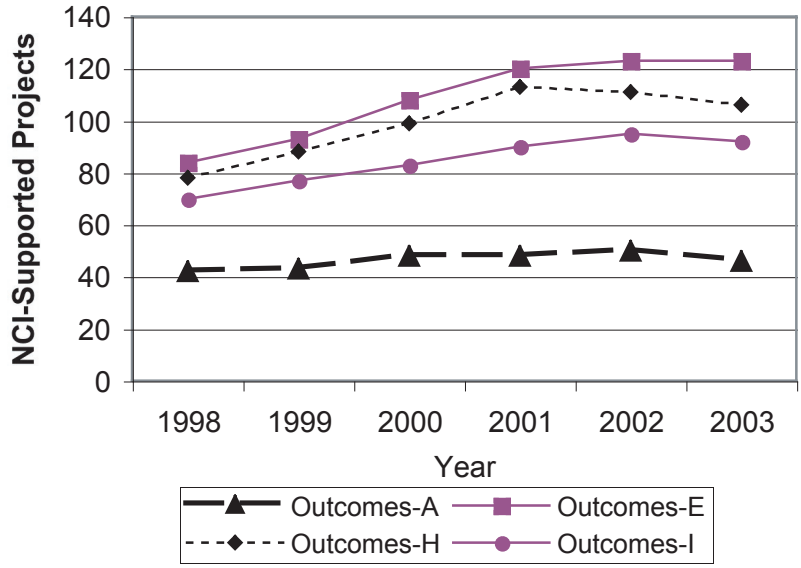
PRG Priorities:

What are the short- and long-term effects of multimodal treatment for breast cancer? (Outcomes-A)

How can we improve patient outcomes, including the physical, emotional, and social dimensions of health-related quality of life? (Outcomes-E)

How can the management of disease symptoms and treatment side effects be improved? (Outcomes-H)

How can the long-term medical and psychosocial outcomes for breast cancer survivors be improved? (Outcomes-I)



NCI Efforts:

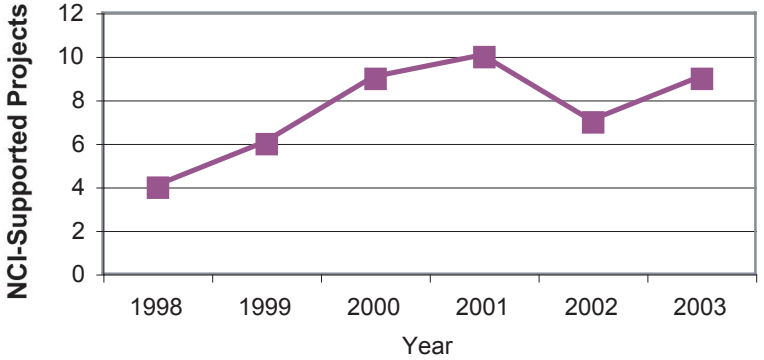
- In FY2003, examples of active areas of investigation relevant to the following priorities included:
  - Outcomes-A: investigating the cognitive deficits experienced by breast cancer patients undergoing systemic chemotherapy versus surgery plus radiotherapy, assessing the impact of breast cancer recurrence on Vietnamese women following various multimodal treatment regimens, and testing the effect of a breast tumor vaccine plus chemotherapy on tumor-specific immunity.

- Outcomes-E: assessing quality of life among minority cancer survivors, interactive cancer communication systems to improve the quality of life of patients and families facing cancer across the disease spectrum, insomnia intervention strategies for breast cancer patients, and using exercise to fight fatigue in breast cancer patients.
- Outcomes-H: the influence of sleep/wake rhythms on patients' tolerance of treatment and quality of life, changes in brain structure and function associated with chemotherapy, healthy weight management strategies for breast cancer survivors, and information for breast cancer survivors on issues that present or persist post treatment.
- Outcomes-I: assessing cognitive effects of chemotherapy treatment in women with breast cancer, the relationship between low-fat diet and breast cancer recurrence, a follow-up study to measure breast cancer survivor's health-related quality of life, and determining the physiologic, psychologic, and social long-term effects of surviving cancer on older adults.

- Examples of clinical trials addressing these priorities included the following:
  - Randomized Study of Health Promotion in Patients Who Are Prostate or Breast Cancer Survivors (DUMC-1547-02-8R4ER)
  - Phase III Randomized Study of Palliative Radiation Therapy for Bone Metastases From Breast or Prostate Cancer (RTOG-9714)
  - Oral Analgesia Regimen for Improved Pain Control in Cancer Patients (E-4Z93)
  - Phase II Study of High-Dose Chemotherapy, Total Body Irradiation, and Autologous Peripheral Blood or Bone Marrow Transplantation in Patients With Hematologic Malignancies or Selected Chemosensitive Solid Tumors (RPCI-DS-9115)
  - On October 19-20, 2000, NCI sponsored *Cancer Survivorship Throughout the Lifespan: Challenges for the 21st Century* to address the complex medical, psychological, and social needs of cancer survivors. A second conference, on June 2-4, 2002, addressed *Cancer Survivorship: Resilience Across the Lifespan*.
  - A report entitled *Meeting the Psychosocial Needs of Women With Breast Cancer*, cosponsored by the NCI, Centers for Disease Control and Prevention, and National Academy of Sciences, was released by the Institute of Medicine in January 2004
- NCI initiatives addressing this priority included Cancer Intervention and Surveillance Modeling Network (CISNET), Cancer Outcomes Measurement Working Group (COMWG), Minority and Underserved Cancer Survivors, Small Grants Program for Behavioral Research in Cancer Control, and Social and Cultural Dimensions of Health.

PRG Priority:

How are the health care needs of breast cancer survivors being met within the current health care system?



NCI Efforts:

- In FY2003, examples of active areas of investigation included telephone therapies that help women cope with breast cancer, assesment of the quality of care provided to Medicare patients with breast cancer, and evaluation of the determinants of quality of care for older breast cancer survivors.
- Examples of clinical trials addressing this priority included the following:

- Randomized Study of Health Promotion in Patients Who Are Prostate or Breast Cancer Survivors (DUMC-1547-02-8R4ER)
- Randomized Study of the Effect of Telephone Counseling by Breast Cancer Survivors on Well-Being of Women With Recurrent Breast Cancer (SWOG-S9832)

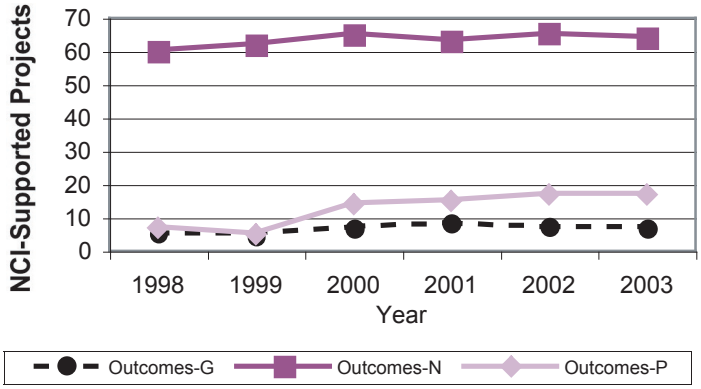
- On October 19-20, 2000, NCI sponsored *Cancer Survivorship Throughout the Lifespan: Challenges for the 21st Century* to address the complex medical, psychological, and social needs of cancer survivors. A second conference, on June 2-4, 2002, addressed *Cancer Survivorship: Resilience Across the Lifespan*.
- NCI initiatives addressing this priority included Minority and Underserved Cancer Survivors, SEER Patterns of Care/ Quality of Care (POC/QOC) Initiative, and Social and Cultural Dimensions of Health.

PRG Priorities:

What treatment research resources exist to foster research on patient-focused outcomes? (Outcomes-G)

What kinds of prevention research resources exist to facilitate patient-focused outcomes research? (Outcomes-N)

What cancer control and survivorship research resources are available to advance the field of outcomes research? (Outcomes-P)

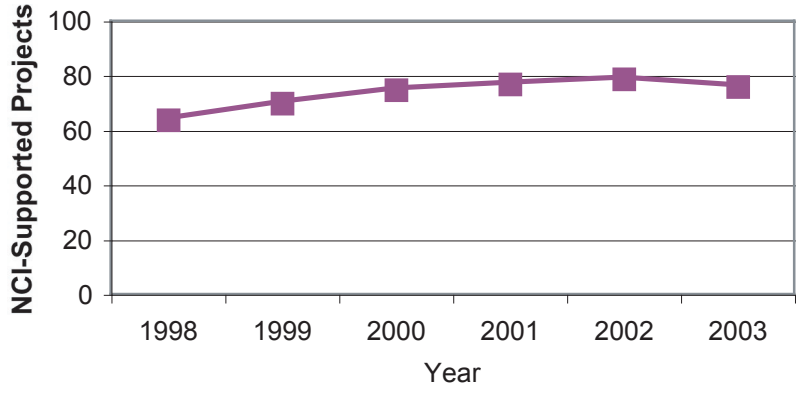


NCI Efforts:

- In FY2003, examples of active areas of investigation relevant to the following priorities included:
  - Outcomes-G: a new functional evaluation tool for cancer care, a cancer chemotherapy program project, and studies to test the effect of adjuvant therapy on long-term survival
  - Outcomes-N: a computerized decision-support tool that educates women about their breast cancer risk factors and risk reduction strategies and numerous Community Clinical Oncology Programs that participate in the Breast Cancer Prevention Trial
  - Outcomes-P: use of HMO data to characterize patterns of care and analyze the relationship between treatment and outcomes for breast cancers, as well as partnerships between NCI-designated Cancer Centers and minority institutions to assess breast cancer outcomes in underserved communities
- NCI initiatives addressing this priority included the CISNET, COMWG, Cancer Surveillance Using Health Claims-Based Data System, Community Clinical Oncology Program (CCOP), and Minority-Based CCOP (MBCCOP).

PRG Priority:

What secondary prevention and health promotion efforts are effective and appropriate for breast cancer patients/ survivors?

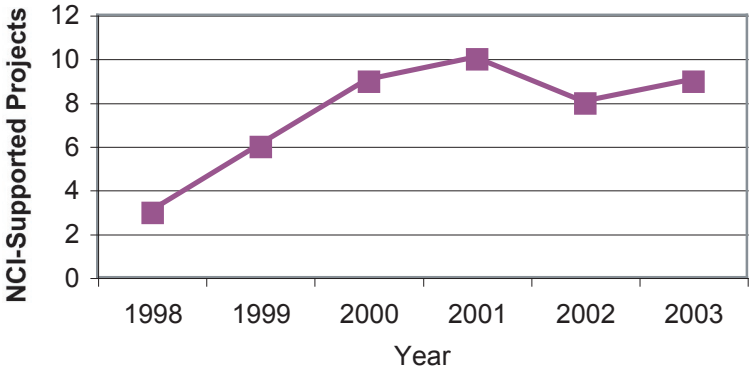


NCI Efforts:

- In FY2003, examples of active areas of investigation included assessing the impact of several dietary factors—including isothiocyanates and d-limonene, vegetables and vegetable juice, and limited fat—on risk of breast cancer recurrence, design of effective interventions for preventing osteoporosis in breast cancer survivors, and the effects of exercise and healthy weight management on quality of life and morbidity in survivors of breast cancer.
- Examples of clinical trials addressing this priority included the following:
  - Phase I Study of Perillyl Alcohol in Women at Risk for Recurrent Breast Cancer (CCF-IRB-3574)
  - Phase II Study of Pentostatin in Patients With Refractory Chronic Graft-Versus-Host Disease (CALGB-100101)
  - Randomized Study of Raloxifene With or Without Exercise Versus Exercise Alone in Women Previously Treated for Breast Cancer (OHSU-6312)
  - Randomized Study of Health Promotion in Patients Who Are Prostate or Breast Cancer Survivors (DUMC-1547-02-8R4ER)
- On October 19-20, 2000, NCI sponsored *Cancer Survivorship Throughout the Lifespan: Challenges for the 21st Century* to address the complex medical, psychological, and social needs of cancer survivors. A second conference, on June 2-4, 2002, addressed *Cancer Survivorship: Resilience Across the Lifespan*.
- NCI initiatives addressing this priority included the Small Grants Program for Behavioral Research in Cancer Control and Minority and Underserved Cancer Survivors.

PRG Priority:

What are the economic and health care outcomes for patients/survivors with breast cancer?

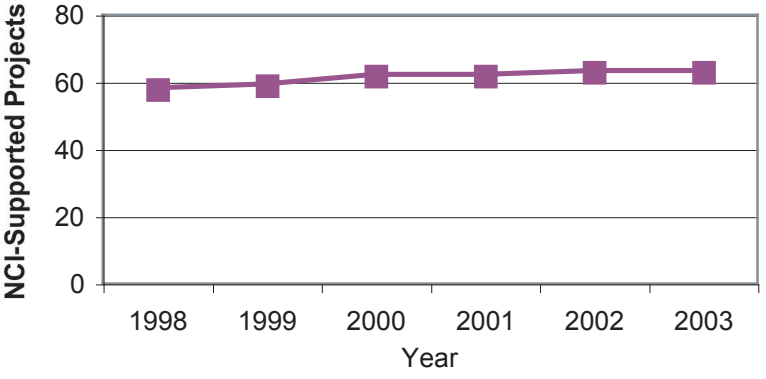


NCI Efforts:

- In FY2003, examples of active areas of investigation included assessing the effectiveness and cost-effectiveness of alendronate on bone mineral density and bone turnover in premenopausal women treated with adjuvant chemotherapy for breast cancer; determining the effects of various treatment strategies on DCIS recurrence rates, survival, costs, and quality of life; and labor market outcomes of long-term breast cancer survivors.
- NCI initiatives addressing this priority included COMWG; Cancer Research Network (CRN); Cancer Surveillance Using Health Claims-Based Data System; and Economic Studies in Cancer Prevention, Screening, and Care.

PRG Priority:

What patient outcomes data are being collected in prevention trials?



NCI Efforts:

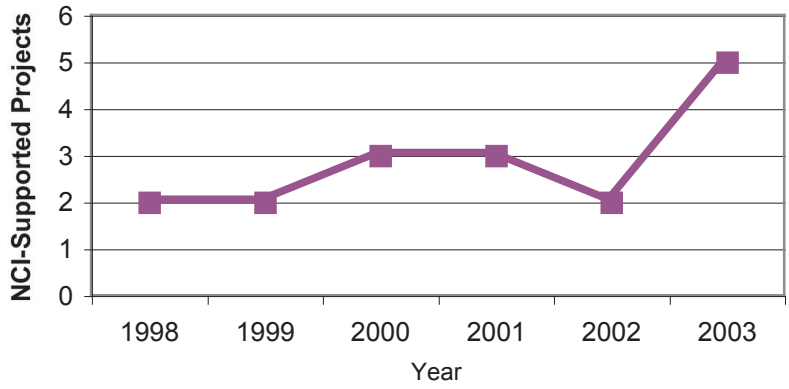
- In FY2003, examples of active areas of investigation included clinical research in cancer treatment and cancer control/prevention through

participation in NCI-supported trials and increasing the availability of protocol-based cancer prevention and control research trials to urban and rural minorities.

- Examples of clinical trials addressing this priority included the following:
  - Phase I Study of Indole-3-Carbinol for the Prevention of Breast Cancer in Nonsmoking Women at High Risk for Breast Cancer (KUMC-8508-01)
  - Phase II Trial of Dietary Fatty Acids: Roles in Hormonally Mediated Cancers in Normal Premenopausal Women (UMN-9509M10234)
  - Pilot Chemoprevention Study of Tamoxifen and Fenretinide in Subjects at High Risk for Developing Invasive Breast Cancer (NCI-94-C-0056L)
- NCI initiatives addressing this priority included the Clinical Trials Cooperative Groups Program and the CCOP.

PRG Priority:

How can patient-focused outcomes for women with advanced metastatic breast cancer be improved?



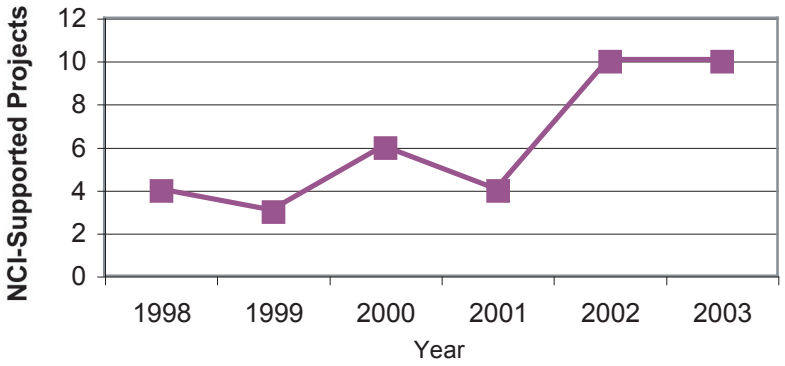
NCI Efforts:

- In FY2003, examples of active areas of investigation included improving pain management in women with breast cancer, assessing symptom occurrence and severity in low-income and racially disparate groups of patients with metastatic breast cancer, and improving palliative care for patients with breast cancer.
- Examples of clinical trials addressing this priority included the following:
  - Phase I Study of Recombinant Vaccinia DF3/MUC1 Vaccine in Patients With Metastatic Breast Cancer (DFCI-97050)
  - Phase II Pilot Study of High Dose Doxorubicin, Cyclophosphamide, Paclitaxel, and Amifostine Followed by Peripheral Stem Cell Rescue in Patients With High-Risk Stage II/III and Responsive Stage IV Advanced Breast Cancer (CHNMC-IRB-99002)
  - Phase II Study of High-Dose Chemotherapy With Autologous Peripheral Blood Progenitor Cell Rescue for Women With Metastatic Breast Cancer, Plus Evaluation of Outpatient Imipenem for Neutropenic Fever (MSKCC-94077)
  - Phase III Randomized Comparison of High Dose Chemotherapy Plus Filgrastim to Filgrastim for Mobilization of Peripheral Blood Stem Cells for Autologous Transplantation for Patients With Responsive Metastatic Breast Cancer or High-Risk Stage II and III Patients (MDA-DM-95047).
- NCI initiatives addressing this priority included the Breast SPOREs

Additional Breast Cancer Outcomes Projects

NCI Efforts:

- Active research projects in FY2003 related to reducing breast cancer health disparities included psychological adjustment among rural breast cancer survivors, quality of life in African-American and Hispanic survivors of breast cancer, and determinants of the quality of care of older breast cancer survivors.



- In FY2003, examples of other active areas of investigation included the relationship between postmenopausal hormone therapy and breast cancer mortality, the risk of developing endometrial cancer and breast cancer as a result of exposure to tamoxifen, enhancing the well-being of individuals recently diagnosed with breast cancer through increased verbal processing of traumatic events, and a computer-based imaging system to reduce anxiety and distress relating to alopecia in women being treated for breast cancer.

The initiatives relevant to research on breast cancer control, survivorship, and outcomes between FY1998 and 2003 include the following list of general initiatives that are described in Table 2-1[5] (Chapter 2) and the category-specific initiatives that are listed and described in Table 8-3.[6]

- Aging Women and Breast Cancer
- Basic and Preclinical Research on Complementary and Alternative Medicine
- Breast and Ovarian Cancer Family Registries (CFRs)
- Breast Cancer Surveillance Consortium (BCSC)
- Cancer Biomedical Informatics Grid (caBIG)
- Cancer Centers Program
- Cancer Genetics Services Directory
- Cancer Research Network
- Cancer Research Training, Career Development, and Education Opportunities
- Clinical Trials Cooperative Group Program
- Community Clinical Oncology Program (CCOP)
- Developmental/Pilot Projects in Cancer Complementary and Alternative Medicine (CAM)
- Exploratory Grants for Correlative Laboratory Studies and Clinical Trials
- Insight Awards to Stamp Out Breast Cancer
- Integrating Aging and Cancer Research
- International Breast Cancer Screening Network

5 Initiatives that impact multiple categories of breast cancer research.

6 Initiatives that are unique to the cancer control, survivorship, and outcomes research category.

- Minority-Based Community Clinical Oncology Program (MBCCOP)
- Minority Institution/Cancer Center Partnership (MI/CCP)
- NCI Center for Bioinformatics (NCICB)
- Small Grants Program for Cancer Epidemiology
- Southern Community Cohort Study (SCCS)
- Special Population Networks
- Specialized Programs of Research Excellence (SPOREs) in Breast Cancer

Table 8-3. NCI Initiatives Relevant to Breast Cancer Research: Cancer Control, Survivorship, and Outcomes[a]

Initiatives With Breast Cancer-Relevant Components

- Basic Biobehavioral Research on Cancer-Related Behaviors (RFA-CA-99-014)
  - Overview: Supports research on the links among biology, behavior, and the environment as they pertain to cancer-related risk behaviors.
  - Relevant Research Projects Resulting From This RFA: Between 1998 and 2003, one project relevant to breast cancer research was supported through this RFA. This project can be found in Appendix B, Table B55, by searching for the RFA number.
- Cancer Control PLANET (http://cancercontrolplanet.cancer.gov/)
  - Overview: A collaborative effort aimed at providing access to data and resources that can help cancer control planners, health educators, program staff, and researchers design, implement, and evaluate evidence-based cancer control programs. It is now being expanded to include tools for primary care clinicians that facilitate the implementation of proven cancer control techniques in practice. Cancer Control PLANET is jointly supported by NCI, the Centers for Disease Control and Prevention (CDC), the American Cancer Society (ACS), the Substance Abuse and Mental Health Services Administration, and the Agency for Healthcare Research and Quality.
  - Relevant Resource Resulting From This Initiative: The Web portal provides access to resources that can assist in:

    Assessing the cancer and/or risk factor burden within a given state

    Identifying potential partner organizations that may already be working with high-risk populations

    Understanding the current research findings and recommendations

    Accessing and downloading evidence-based programs and products

    Finding guidelines for planning and evaluation
- Cancer Intervention and Surveillance Modeling Network (CISNET) (http://cisnet.cancer.gov/about)
  - Overview: A consortium of NCI-sponsored researchers whose focus is to use modeling techniques to describe the impact of prevention, screening, and/or treatment interventions in population-based settings.

a Lists of the projects derived from each initiative can be located on the online Supplement to the Breast Cancer Progress Report: Initiative Database.

- Relevant Projects Resulting From This Initiative: There are currently seven funded projects within the consortium that focus on breast cancer:

  Breast Cancer Trend Analysis Using Stochastic Simulation

  Breast Cancer: Role of Early Detection, Treatment, and Prevention

  Cancer Intervention and Surveillance Modeling Network (CISNET)

  Mechanistic Modeling of Breast Cancer Surveillance

  Outcomes Across the Spectrum of Breast Cancer Care

  Simulating Breast Cancer in Wisconsin

  Surveillance of Breast Cancer Trends by MISCAN

  Specific projects can be found in Appendix B, Tables B7, B9, B31, B41, B43, B51, B52, and B58, by searching for the RFA number (CA99-013).

- Cancer Outcomes Measurement Working Group (COMWG) (http://outcomes.cancer.gov/methods/measures/comwg)
  - Overview: Members of COMWG evaluate existing endpoint measures, including health-related quality of life, economic burden, and patient satisfaction. They also work to formulate alternative strategies for identifying valid, reliable, sensitive, and feasible clinical and patient-centered endpoint measures for use in quality of cancer care studies. Thirty-five members of the working group were selected to provide expertise in outcomes measurement for four cancer sites, including breast cancer.
  - Relevant Resource Resulting From This Initiative: Findings of the Working Group have been reported to the NCI and will be published as the book *Outcomes Assessment in Cancer*.
- Cancer Surveillance Using Health Claims-Based Data System (http://dccps.nci.nih.gov/ARP/research/health.asp)
  - Overview: Support for research to investigate the utility of health claims information as a reporting source for assessing the national cancer burden.
  - Relevant Projects Resulting From This Initiative: Between 1998 and 2003, five projects relevant to breast cancer research were supported through this initiative. Specific projects can be found in Appendix B, Tables B49, B52, and B53, by searching for the PA number (PA-99-015).
- Cancer Survivorship Studies in Established Epidemiologic Cohorts (PA-98-027)
  - Overview: Fosters research on issues related to long-term cancer survivorship through the use of existing epidemiologic study populations, particularly in the areas of specific health or lifestyle outcomes and their modulation by common risk factors and other exposures.
  - Relevant Research Projects Resulting From This PA: Between 1998 and 2003, three projects relevant to breast cancer research were supported through this PA. Specific projects can be found in Appendix B, Tables B2, B29, and B30, by searching for the PA number.
- Centers for Complementary and Alternative Medicine Research (RFA-AT-00-001)
  - Overview: Research conducted at these centers will examine the potential efficacy, safety, and validity of complementary and alternative medicine practices, as well as the physiological or psychological mechanisms underlying or contributing to the effects of these practices.

- Relevant Resources Resulting From This Initiative: The National Center for Complementary and Alternative Medicine (NCCAM) Web site provides information on complementary and alternative medicine practices, advisories, treatment options, clinical trials, and funding information. Seven NCCAM clinical trials are applicable to breast cancer:

  Acupuncture for Shortness of Breath in Cancer Patients

  Distance Healing in Wound Healing after Breast Reconstruction Surgery

  Macrobiotic Diet and Flax Seed: Effects on Estrogens, Phytoestrogens, & Fibrinolytic Factors

  Massage Therapy for Breast Cancer Treatment-Related Swelling of the Arms and Legs

  Massage Therapy for Cancer-Related Fatigue

  Mistletoe Extract and Gemcitabine for the Treatment of Solid Tumor Cancers

  Pycnogenol for the Treatment of Lymphedema of the Arm in Breast Cancer Survivors

- Centers of Excellence in Cancer Communication Research (http://dccps.nci.nih.gov/eocc/ceccrs_index.html)
  - Overview: Supports research and outreach aimed at increasing knowledge of, access to, and use of cancer communication tools by the public, patients, survivors, and health professionals. These Centers provide essential infrastructure to facilitate rapid advances in knowledge about cancer communications, translate theory and programs into practice, and train health communication scientists.
  - Projects Resulting From This Initiative: Four academic institutions were established as Centers of Excellence in Cancer Communication Research in 2003. The following Centers are actively pursuing breast cancer-relevant projects:

    Saint Louis University: Capture on videotape the stories of 80 African-American breast cancer survivors, examine the effectiveness of these stories in promoting mammography in 900 African-American women, and test a new explanatory model of narrative cancer communication effects

    University of Michigan: A multiphased experimental process to explore methods of communicating risk regarding tamoxifen prophylaxis to women at high risk for breast cancer

    University of Wisconsin, Madison: Controlled trial will examine whether breast cancer patient outcomes change as different types of conceptually distinct CHESS (Comprehensive Health Enhancement Support System) services (information, social support, and skills training) are systematically added to a patient's treatment resources

- Digital Divide Pilot Projects (http://cancercontrol.cancer.gov/eocc/ddpp_awards.html)
  - Overview: Supports research and programs to understand and eventually breach the Digital Divide that exists among many minority populations in accessing and utilizing cancer information on the Internet.
  - Relevant Projects Resulting From This Initiative: In collaboration with NCI's North Central and Mid-West Regions Cancer Information Service (CIS), the University of Wisconsin and the Karmanos Cancer Center will expand the CHESS Program that puts personal computers and Web-based support resources into the homes of African-American breast cancer patients.
- Economic Studies in Cancer Prevention, Screening and Care (http://cancercontrol.cancer.gov/ARP/research/economic.asp)
  - Overview: Supports research directed toward increasing knowledge of the economic aspects of cancer prevention, screening, and care.

- Relevant Projects Resulting From This Initiative:

  Long-Term Cost and Outcomes of Breast Cancer Screening

  Tamoxifen & Breast Cancer—Acceptance/Cost Effectiveness

  Use of Cancer Screening in a Managed Care Environment

- Exploratory Grants for Behavioral Research in Cancer Control (PA-99-163)
  - Overview: Supports the development of novel or conceptually creative ideas that may produce innovative advances in the behavioral sciences, specifically in the areas of cancer prevention and control.
  - Relevant Research Projects Resulting From This PA: Between 1998 and 2003, 12 projects relevant to breast cancer research were supported through this PA. Specific projects can be found in Appendix B, Tables B45, B51, and B53-55, by searching for the PA number.
- Health Communications in Cancer Control (RFA-CA-98-014)
  - Overview: Supports research on the use of interactive digital media in cancer prevention and control and promotes the refinement of communications systems to improve dissemination of cancer control-related information.
  - Relevant Research Projects Resulting From This RFA: Between 1998 and 2003, three projects relevant to breast cancer research were supported through this RFA. Specific projects can be found in Appendix B, Table B51, by searching for the RFA number.
- Long-Term Cancer Survivors: Research Initiatives (RFA-CA-04-003)
  - Overview: Promotes and supports research that will lead to the decrease in physiologic and psychosocial morbidity and mortality associated with long-term (over 5 years) survival from cancer.
  - Relevant Research Projects Resulting From This RFA: Between 1998 and 2003, three projects relevant to breast cancer research were supported through this RFA. Specific projects can be found in Appendix B, Tables B40, B49, and B51, by searching for the RFA number and the previously issued number (RFA-CA-97-018).
- Minority and Underserved Cancer Survivors (http://cancercontrol.cancer.gov/ocs/underserved)
  - Overview: Supports supplements to NCI-designated Cancer Centers for research on cancer survivorship among minority and underserved cancer populations in community settings.
  - Relevant Projects Resulting From This Initiative:

    Breast Cancer Survivors & Community Support

    Follow-Up Care in Breast Cancer Survivors

    Reproductive Health in African-American Breast Cancer Survivors
- Research on the Impact of Cancer on the Family (http://dccps.nci.nih.gov/bb/research_family.html)
  - Overview: Supports supplemental awards to NCI-funded Clinical and Comprehensive Cancer Centers to expand the study of the impact of cancer on the family.
  - Relevant Projects Resulting From This Initiative: Studies at ten institutions were funded that spanned the life cycle, focusing on both child and adult caregivers, and addressed multiple cancer sites, including breast, colon, prostate, brain, head and neck, and pediatric cancers.

- Research Supplements for Underrepresented Minorities (http://cancercontrol.cancer.gov/ocs/underrepresented/)
  - Overview: Supplements research support to: (1) reach out to minority graduate and undergraduate students studying biomedical or behavioral sciences; and (2) provide an opportunity to develop research capabilities.
  - Relevant Projects Resulting From This Initiative: Five projects are supported through this program, most of which are generally applicable to behavioral, survivorship, and communication research. The following project is directly related to breast cancer research:

    Young Breast Cancer Survivors: A Population-Based Cohort
- SEER-Medicare Linked Database (http://healthservices.cancer.gov/seermedicare)
  - Overview: Supports a large database that incorporates two large population-based sources of data that provide detailed information about elderly persons with cancer. The data come from the Surveillance, Epidemiology, and End Results (SEER) program of cancer registries that collect clinical, demographic, and cause-of-death information for persons with cancer and the Medicare claims for covered health care services from the time of a person's Medicare eligibility until death.
  - Relevant Resource Resulting From This Initiative: The SEER-Medicare Linked Database Web site includes a section on analytic support to assist researchers who use the database.
- SEER Patterns of Care/Quality of Care (POC/QOC) Initiative (http://cancercontrol.cancer.gov/bb/seer_pattern.html)
  - Overview: Evaluates the dissemination of state-of-the-art therapy into community practice, disseminates findings in scientific journals and professional meetings, and works with professional organizations to develop relevant educational or training opportunities.
  - The SEER registries perform POC/QOC studies every 3 to 5 years for the major cancer sites (including breast). Cancer sites with emerging new treatments or concerns regarding provision of state-of-the-art therapy would be conducted in alternate years.
- Small Grants Program for Behavioral Research in Cancer Control (http://dccps.nci.nih.gov/smallgrants/index.html)
  - Overview: Designed to encourage investigators from a variety of academic, scientific, and public health disciplines to apply their skills to behavioral research investigations in cancer prevention and control.
  - Relevant Research Projects Resulting From This Initiative: Between 1998 and 2003, 30 projects relevant to breast cancer research were supported through this initiative. Specific projects can be found in Appendix B, Tables B9, B10, B12, B33, B41, B43, B47, and B51, by searching for the PA numbers (PAR-02-037 and PAR-99-006).
- Social and Cultural Dimensions of Health (PA-02-043)
  - Overview: Encourages further development of health-related social sciences.
  - Relevant Projects Resulting From This PA: Pending—this PA will remain open until December 21, 2004.
- Surveillance, Epidemiology and End Results (SEER) (http://seer.cancer.gov)
  - Overview: Database of information on cancer incidence and mortality. SEER currently collects and publishes data from 11 population-based cancer registries and 3 supplemental registries. Approximately 26% of the U.S. population is represented, including a substantial portion of racial/ethnic minorities and other medically underserved individuals.
  - Relevant Resource Resulting From This Initiative: SEER recently published the *Annual Report to the Nation on the Status of Cancer, 1975-2000*, which updates statistics on four main cancer types, including breast.

- Translating Research into Improved Outcomes (TRIO) (http://cancercontrol.cancer.gov/bb/trio.html)
  - Overview: Supports efforts to move research discoveries through program development into evidence-based service delivery. Three overarching goals include: (1) closing the discovery-delivery gap by disseminating cancer and behavioral surveillance data to identify needs, track progress, and motivate national, state, and local action; (2) collaborating with public health, clinical practice, and voluntary organizations to reduce the overall cancer burden and eliminate cancer health disparities; and (3) working with national, regional, state, and local partner organizations to identify and overcome the infrastructure barriers to the adoption of evidence-based cancer control programs and practices.
  - Relevant Resource Resulting From This Initiative: TRIO supports communication efforts in breast cancer screening through the breast cancer screening section of the Cancer Control PLANET Web portal and the NCI/USDA/ACS/CDC collaboration in eight states promoting breast and cervical cancer screening among women never or rarely screened who live in high-mortality counties.

Ongoing NCI Research: Recent Progress in Breast Cancer Control, Survivorship, and Outcomes

The Importance of Mammography

Early detection of breast cancer through periodic examinations and mammography is considered the most effective method of breast cancer control. Although breast cancer screening methods have advanced substantially in the last few years, these are only of benefit to women who are actually screened. Recent research has shown that women are more likely to obtain a mammogram if they receive tailored communications. Specifically, women who receive targeted educational materials or telephone counseling are up to 20% more likely than women receiving standard care to obtain a mammogram within the recommended period (Champion et al., 2003; Clark and Wold, 2002; McCaul and Wold, et al., 2002). Although telephone and mailed reminders have both been tested, the most effective methods to encourage screening are combined interventions in which women receive written communications as well as motivational telephone interviews or in-person counseling with a letter from a physician (Champion et al., 2003; Valanis et al., 2003; Legler et al., 2002).

Advances in education have helped increase the use of mammography; in 1998, almost 70% of U.S. women age 40 or older reported receiving a mammogram within the last 2 years, compared with less than 30% of women in 1987 (Legler et al., 2002; Swan et al., 2003). As a result, mammography was the only type of cancer screening test for which the *Healthy People 2000*[7] goal was reached. Unfortunately, not all populations have experienced these dramatic improvements, as older individuals, those with less education, and those with lower incomes are still less likely to be screened than other women (Hiatt et al., 2002; Meissner et al., 2003). In addition, while differences in mammography rates have narrowed between Caucasian and African-American women in recent years, rates for Hispanic women remain lower than those of either group (Legler et al., 2002). This issue remains important for our nation because, among women with late-stage cancer, over 50% have not undergone screening (Taplin et al., 2004 in press). To approach the mortality reduction goals for the year 2010, we must screen women of all backgrounds and reach those who have not been screened.

Factors Affecting the Accuracy of Mammography

Although screening mammography is the best technique available for reducing mortality from breast cancer, mammography does not detect every breast cancer. Much has been learned in recent years about some of the factors that affect the ability of mammography to accurately detect cancer. We now know, for example, that in a population offered screening, 40% of late-stage cancers occur among women who have had negative screening tests within the previous 3 years (Taplin et al., 2004).

7 Healthy People 2000 is available at http://odphp.osophs.dhhs.gov/pubs/hp2000.

One key factor is breast density, which makes the interpretation of mammograms challenging because dense breast tissue can resemble cancerous tissue on mammographic film (Carney et al., 2003; Mandelson et al., 2000; Rosenberg et al., 1998). Breast density appears to be associated with several factors, including age, race, and hormone usage. Breast density decreases with age, so it is perhaps not surprising that the accuracy of mammography increases with age (Barlow et al., 2002; Carney et al., 2003; Rosenberg et al., 1998; Ziv et al., 2003). Asian and black women are more likely than white women to have dense breasts, although black and white women over 65 have similar breast density (El-Bastawissi et al., 2001). However, researchers found that screening mammography is as accurate in black women as in white women after controlling for age, breast density, and time since the previous mammogram (Gill and Yankaskas, 2004). Women who use hormone replacement therapy (HRT) are two to three times as likely as women who do not use HRT to have dense breasts, but these differences decrease when HRT use is stopped (Rosenberg et al., 1998; Rutter et al., 2001). The impact of HRT on mammography accuracy appears to be completely attributable to the fact that HRT use increases breast density (Carney et al., 2003).

Another factor that influences the quality of the screening process is breast positioning during the mammogram procedure. Specifically, mammograms are up to 20% more likely to detect cancers when the breast is positioned properly on the machine, and women with cancers found after a negative mammogram result are more than twice as likely to have been positioned improperly at the time of the screening examination (Taplin et al., 2002).

Quality of Care

Although a vast literature addresses the use of screening mammography for breast cancer, less attention has been devoted to follow-up of abnormal test results. Recent research has begun to address this gap, showing that over 25% of patients with an abnormal screening mammography result do not receive the recommended follow-up care. Thus, barriers to appropriate follow-up exist at the provider, patient, and health care system levels (Yabroff et al., 2003). Rates of inappropriate follow-up are even higher in some populations, as almost one-third of black women with an abnormal mammogram or clinical breast exam do not receive appropriate follow-up 6 months after being screened (Kerner et al., 2003).

Treatment provided to women with early-stage breast cancer appears to be consistent with the results of national consensus conferences and clinical trials addressing this topic (Guadagnoli et al., 1998; Harlan et al., 2002); however, some disparities remain in the care of women with breast cancer. For example, women of low socioeconomic status are more likely than others to be diagnosed with late-stage cancer, to experience a recurrence, and to die from breast cancer (Bradley, Given, et al., 2002; Gordon, 2003). In addition, elderly women enrolled in an HMO are less likely to have breast cancer diagnosed at a late stage and more likely to receive breast-conserving therapy than women enrolled in a fee-for-service setting (Riley et al., 1999). However, other disparities have decreased. Specifically, investigators have shown that African-American women tend to be diagnosed with breast cancer at the same stage, receive the same treatment, and have the same survival rates as white women after controlling for several patient characteristics, such as age, disease stage, socioeconomic status, and insurance coverage (Bradley, Given, et al., 2002; Gordon, 2003). Furthermore, disabled women have the same risk of dying from breast cancer as women who are not disabled (Roetzheim and Chirikos, 2002).

Survivors' Issues

Women with a history of breast cancer account for over 40% of all female cancer survivors. As the number of breast cancer survivors increases, it is becoming increasingly apparent that these women are much more resilient than previously assumed.

Breast cancer survivors report a broad range of physical symptoms after completing treatment (Michael et al., 2000). Some groups of women are at greater risk for adverse effects following breast cancer diagnosis and treatment; women who have had adjuvant chemotherapy and those who are younger appear to be more likely than other women to experience problems with general health, physical functioning, and social functioning (Ganz et al., 2002).

Behavioral research has demonstrated that social support mediates individuals' general well-being, and this may be particularly true after a cancer diagnosis. An analysis of data from the Nurses' Health Study found that level of social integration is an important predictor of subsequent health-related outcomes for breast cancer survivors—even more than treatment or tumor characteristics. On average, socially isolated women were more adversely affected by breast cancer than socially integrated

women in terms of their role function, vitality (feeling energetic and alert), and physical function. Rehabilitation programs should emphasize interventions that address the availability of adequate social support (Michael et al., 2002).

It now appears that the threat to life imposed by cancer can be life altering, especially with respect to health behaviors. In one study examining this effect, researchers found that after their cancer diagnosis, almost half of smokers quit smoking, and a similar proportion of study participants improved their dietary habits; however, one-third exercised less (Blanchard et al., 2003). Several researchers are studying the risk for physical inactivity following cancer and its corresponding adverse impact on weight and health; these researchers are using exercise interventions to improve survivors' emotional and functional well-being. The results for breast cancer survivors are compelling: exercise training programs have beneficial effects on cardiopulmonary function and quality of life (Courneya, Mackey, et al., 2003; Pinto et al., 2003), reduce fatigue, and help maintain functional ability (Kolden et al., 2002), and, when combined with group psychotherapy, may improve women's quality of life beyond the benefits of group therapy alone, especially with respect to physical and functional outcomes (Courneya, Friedenreich, et al., 2003). While it is not clear if these types of interventions will alter the course of cancer (i.e., rate of or time to recurrence or death), such programs hold promise for reducing cancer-related morbidity and promoting general health. They also appear to have enormous appeal to survivors eager to reduce the perceived stress in their lives and take control of their bodies after cancer.

As the number of long-term survivors increases, the indirect morbidity and disability costs of breast cancer may also be rising. Research indicates that breast cancer has an economic impact on long-term survivors. In one study, survivors who were working when they were originally diagnosed experienced much larger reductions in their annual earnings over 5 years than working control subjects (Chirikos et al., 2002). Breast cancer survivors are also 10% less likely to be working than women without breast cancer. However, women who survive breast cancer and continue to work report working approximately 3 more hours a week than women who do not have cancer. This suggests that the morbidity associated with certain types and stages of breast cancer and its treatment does not interfere with a woman's ability to work (Bradley, Bednarek, et al., 2002).

Continuing Needs and Evolution

In spite of recent progress, most women in the United States still do not obtain recommended annual mammograms. Advances are clearly needed in communications strategies to educate more women about the importance of mammography. More research is also needed on barriers to screening and ways to reduce them to ensure that all women are screened at recommended intervals. Furthermore, mechanisms need to be identified to reduce health disparities by increasing the rate at which underserved populations receive mammography screening. Disparities in treatment, including likelihood of receiving breast-conserving surgery and outcomes of various breast cancer treatments, also require further exploration. In addition, we need new screening techniques that are more sensitive and specific than mammography and that offer improved data storage, transmission of results, cost, and ease of use. Because the accuracy of individual radiologists in interpreting mammograms varies (depending on such factors as training, experience, and type of screening program), more research is needed on sources of variation and ways to increase radiologists' accuracy.

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