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]

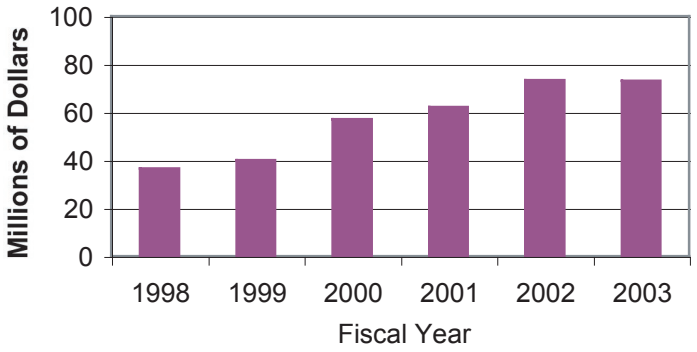
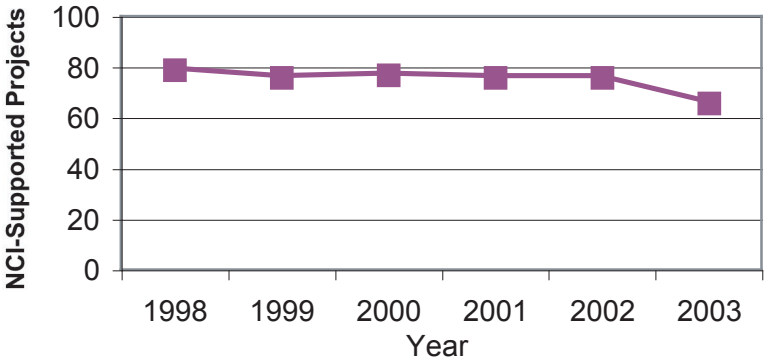


Figure 6-1. NCI's extramural investment in research on breast cancer early detection, diagnosis, and prognosis: 1998-2003 (in millions of dollars)

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.

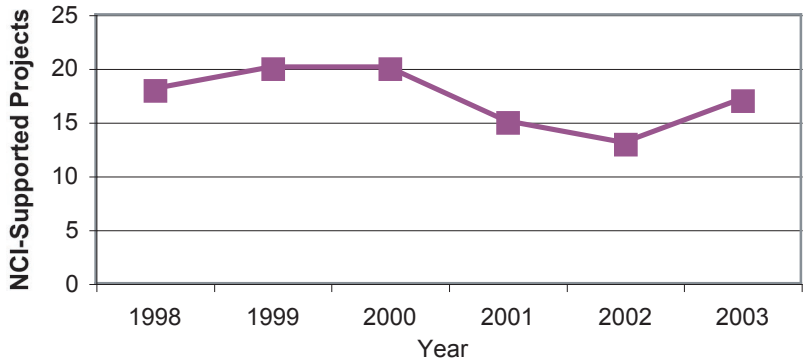
1 A project may map to more than one PRG priority and therefore be represented in more than one figure. Projects active in 2003 are listed in Appendix B (Tables B-24 to B-32) by Principal Investigator's name for each PRG priority.

- 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?

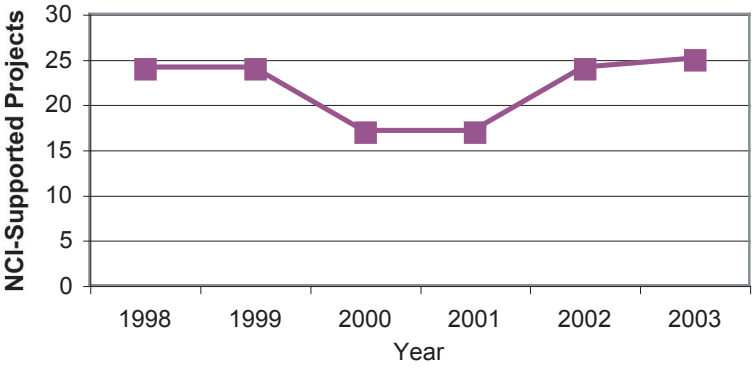


NCI Efforts:

- 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?

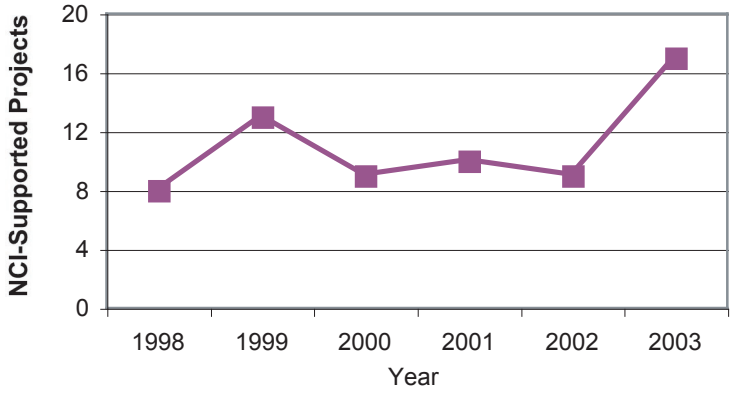


NCI Efforts:

- 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:

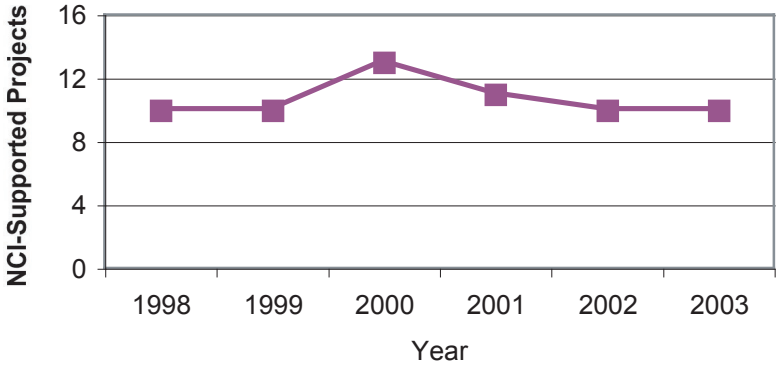
- In FY2003, examples of active areas of investigation included near-infrared-emitting, fluorochrome-conjugated metabolite probes capable of imaging *in vivo* metabolic function in real time, monitoring tumor neovascularity using contrast-enhanced ultrasound imaging modes, estrogens labeled with fluorine-18 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?

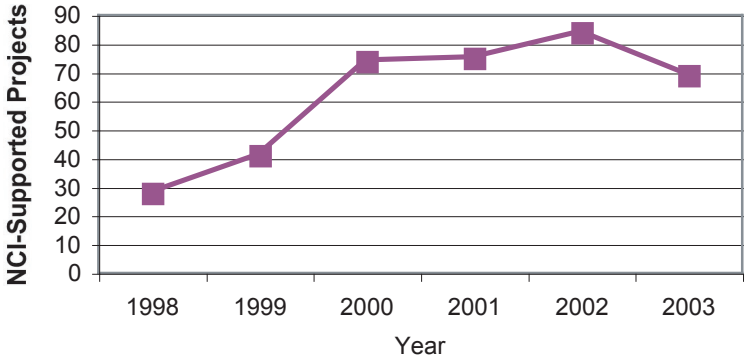


NCI Efforts:

- 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).



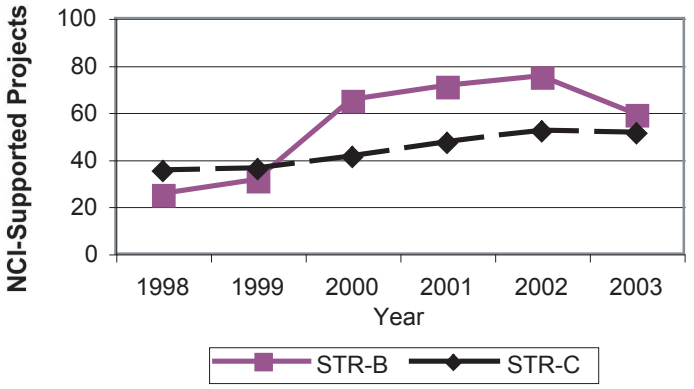
NCI Efforts:

- 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:

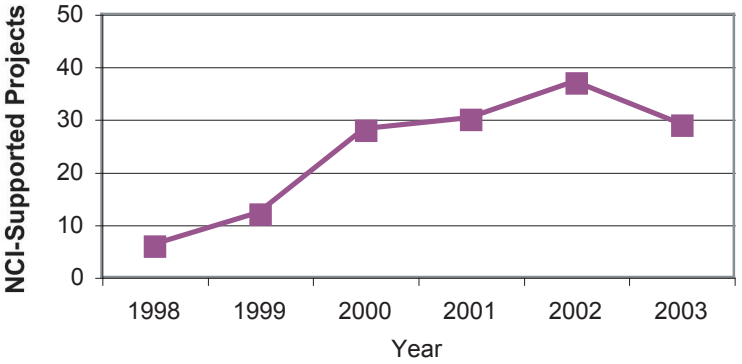
- In FY2003, examples of active areas of investigation relevant to the following priorities included:
  - Both STR-B and STR-C: the development of markers of apoptosis and cell proliferation, a probe for accurate sentinel node localization without the need for the radioactive technetium tracer, *in vivo* 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

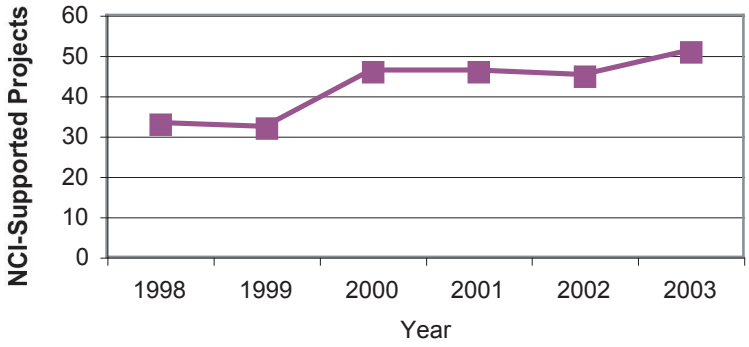


diagnostic tests for breast cancer, prognostic modeling for patients with high-risk primary breast cancer, and assays using expression-based markers to detect circulating breast cancer cells.

- 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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