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]

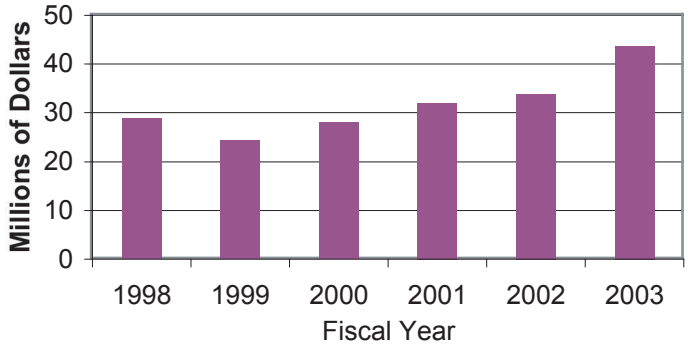


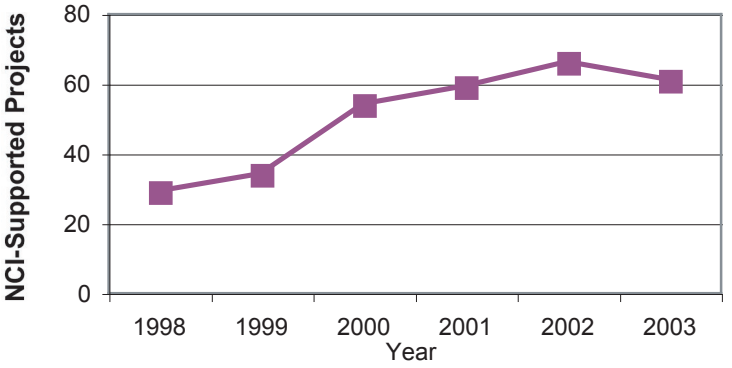
Figure 5-1. NCI's extramural investment in breast cancer prevention research: 1998-2003 (in millions of dollars)

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.

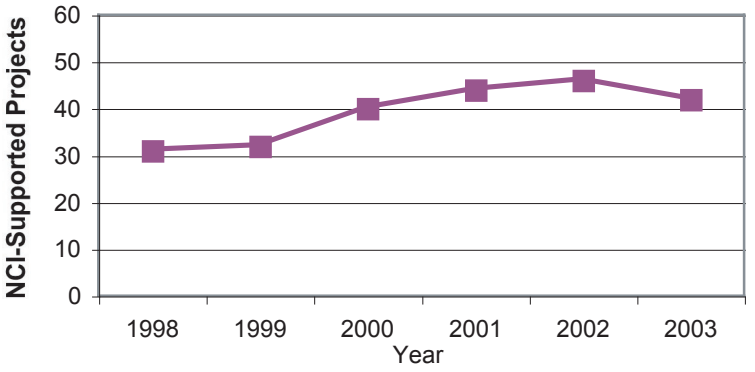


NCI Efforts:

- 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.



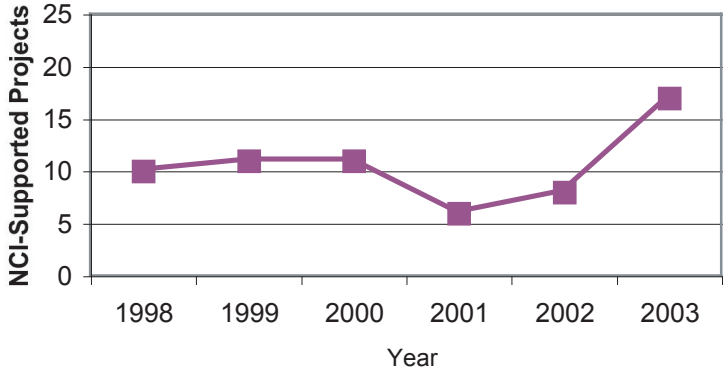
NCI Efforts:

- 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.

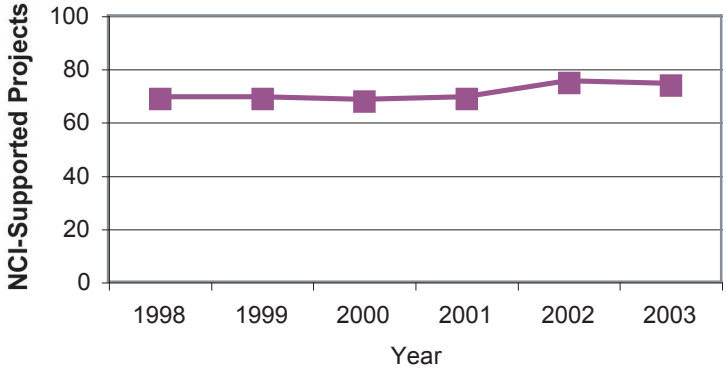


NCI Efforts:

- 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.



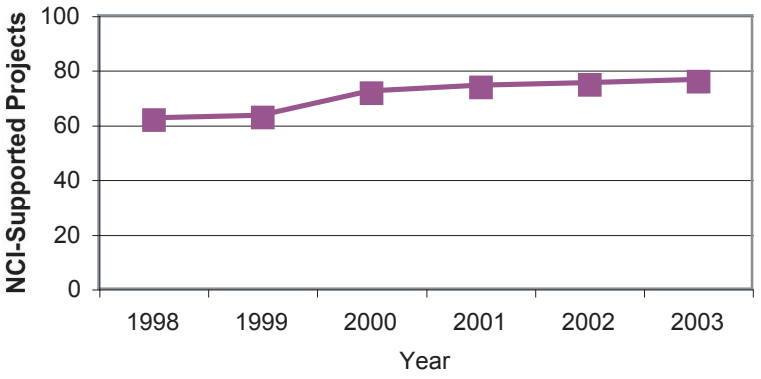
NCI Efforts:

- 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).

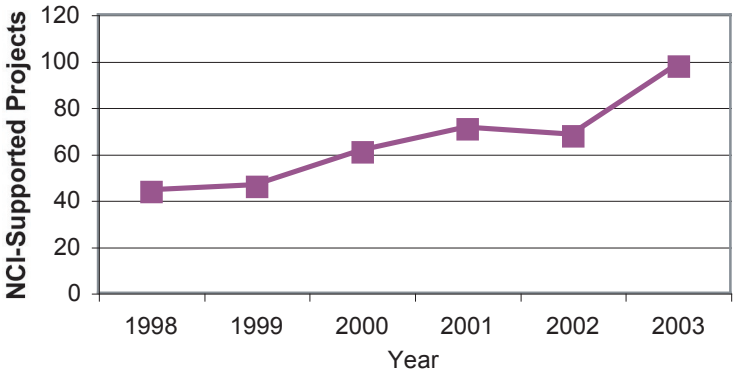


NCI Efforts:

- 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?

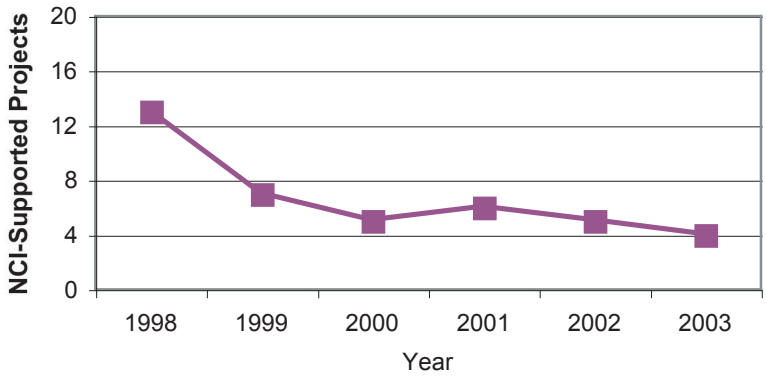


NCI Efforts:

- 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?

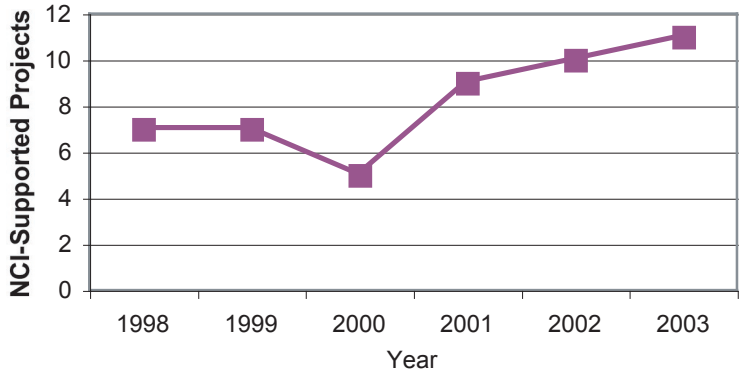


NCI Efforts:

- 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)

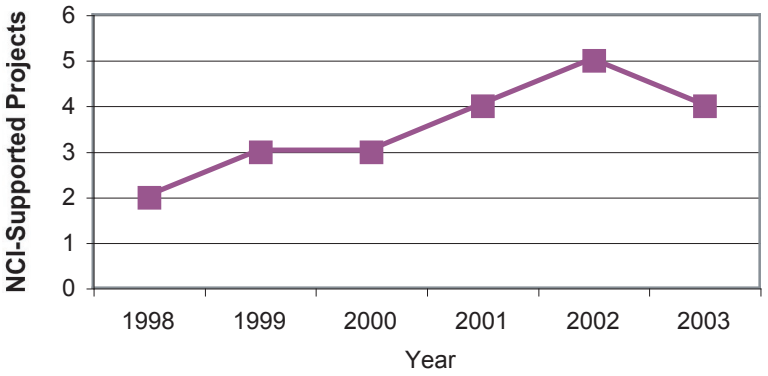
a This priority was part of the Genetics section in the original Breast Cancer PRG report.

- 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]



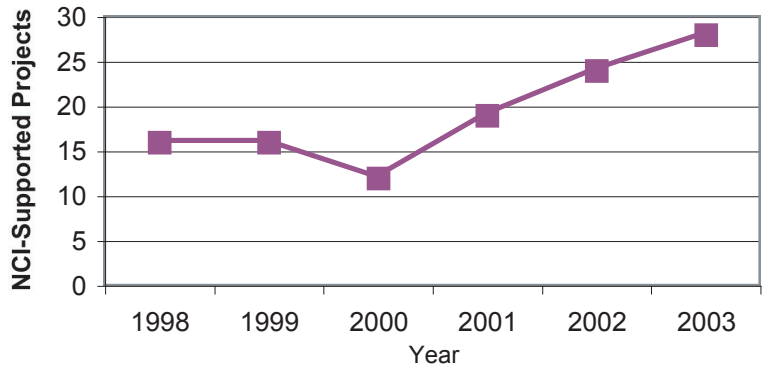
NCI Efforts:

- 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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