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]

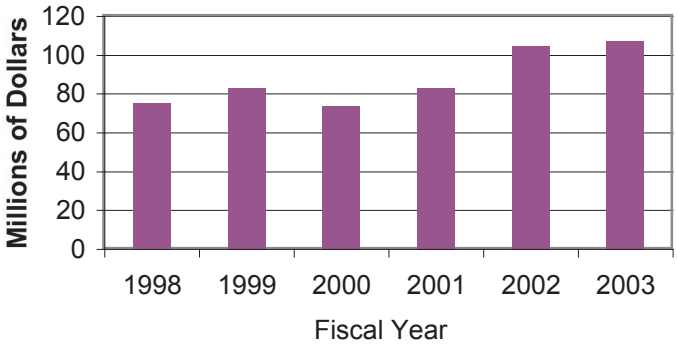


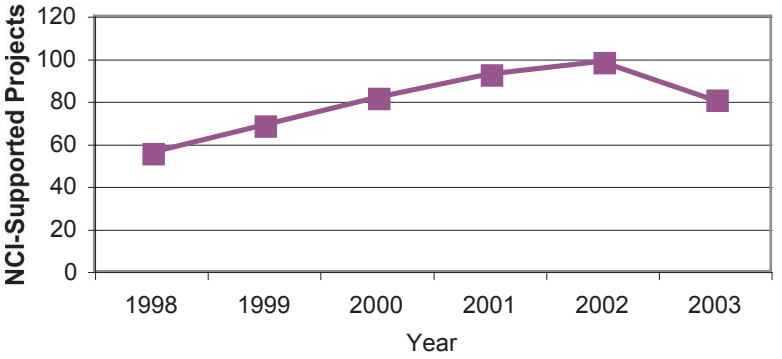
Figure 4-1. NCI's extramural investment in breast cancer etiology research: 1998-2003 (in millions of dollars)

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?

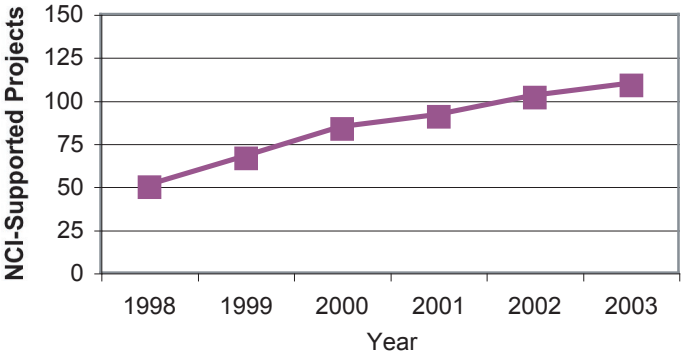


NCI Efforts:

- 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.

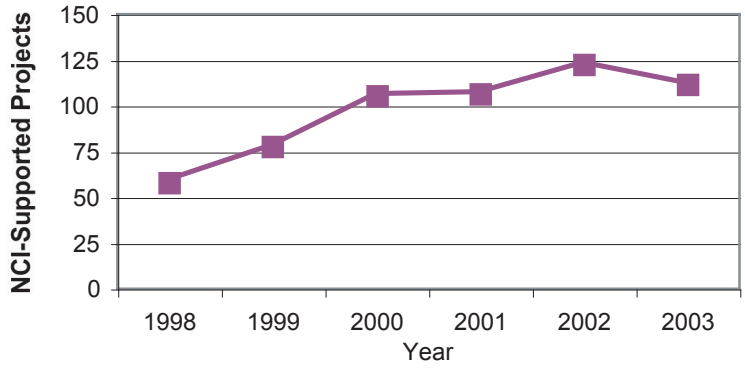
b. This priority merges the two original PRG priorities: "What are the best approaches to understanding gene-environment interactions?" from the Etiology section and "Do any life experiences, behaviors, or environmental exposures influence breast cancer risk among women with inherited mutations in major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

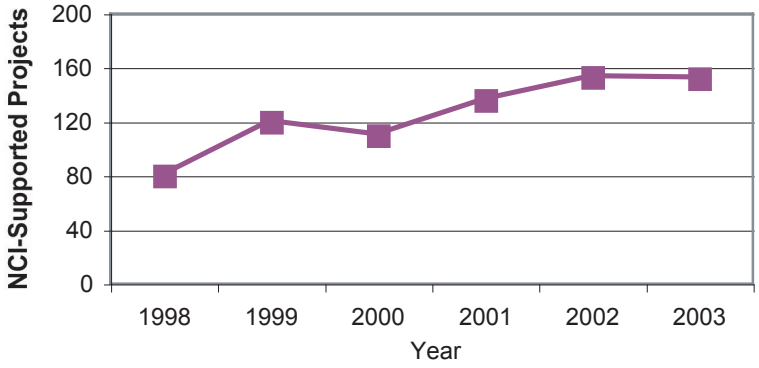


- In FY2003, examples of active areas of investigation included the association between recurrence of breast carcinoma *in situ* and modifiable lifestyle factors, post-treatment behavioral risk factors for recurrence of secondary breast tumors or new primaries, regulation of breast cancer growth by activation 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?

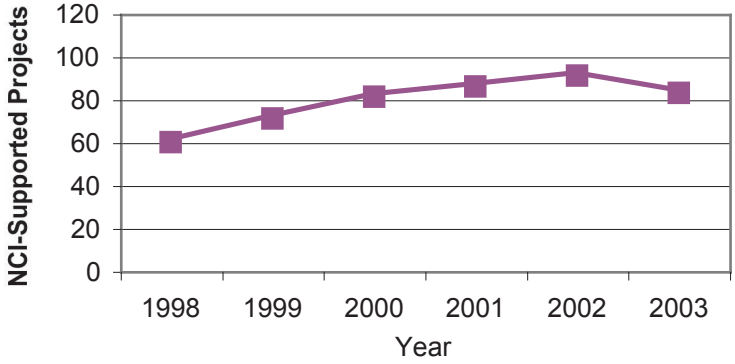
NCI Efforts:



- 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?

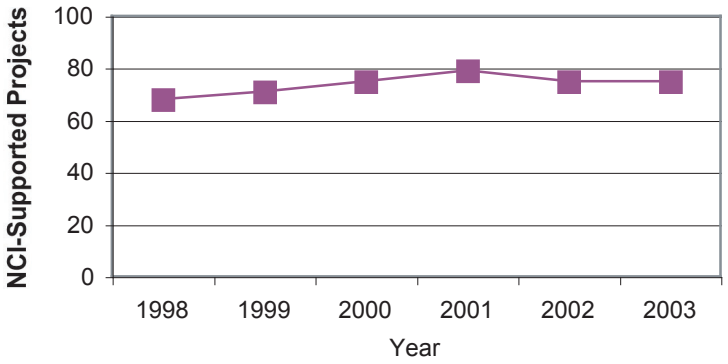


NCI Efforts:

- 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.

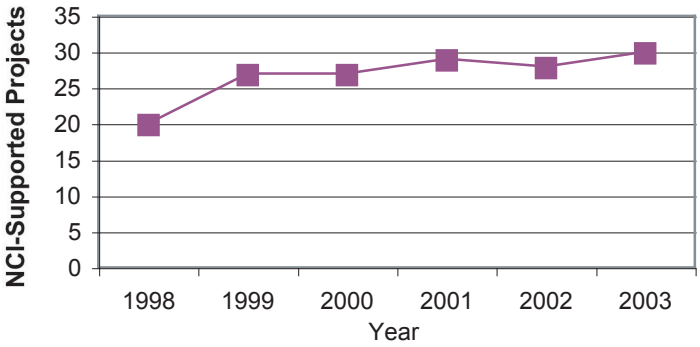
Additional Breast Cancer Etiology Projects

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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