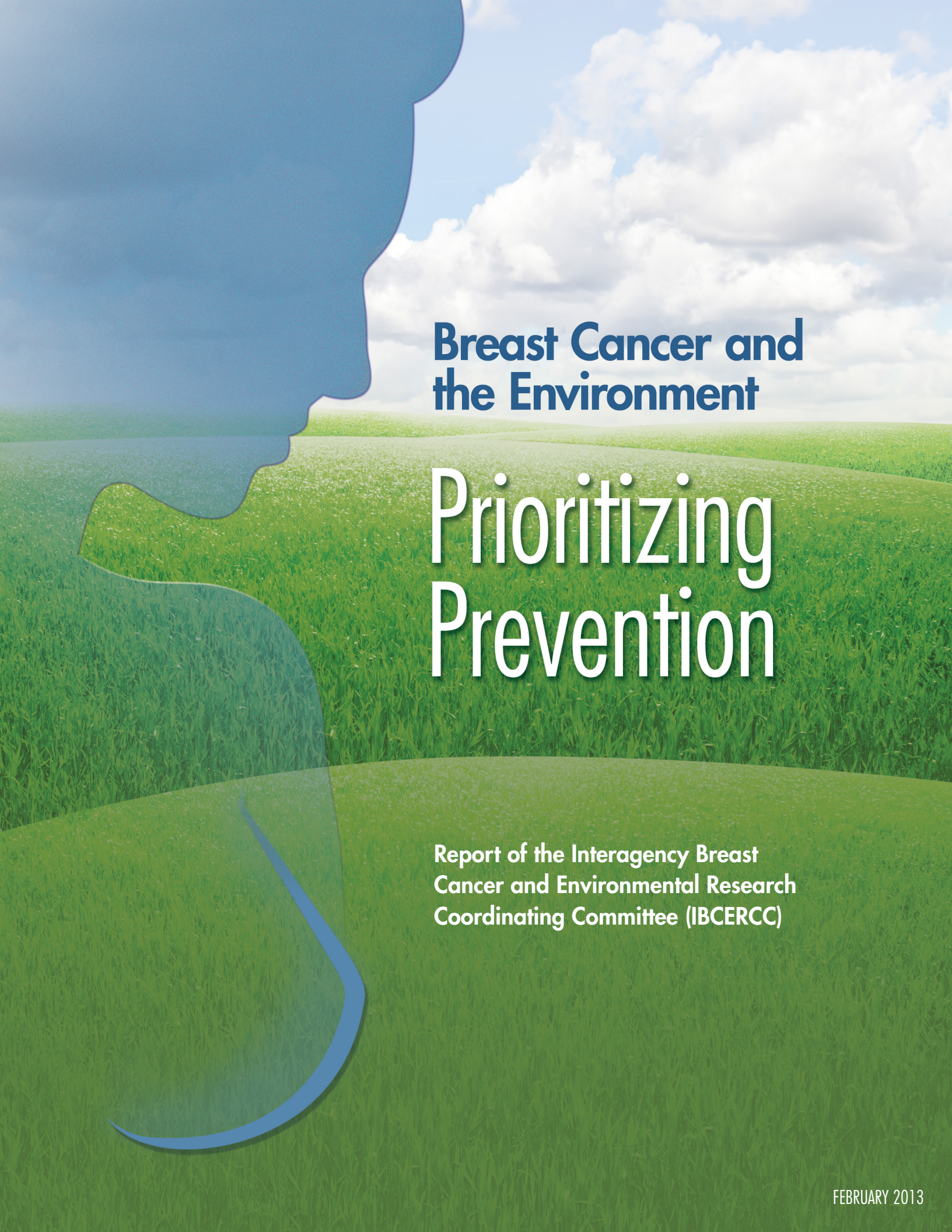

Breast Cancer and the Environment

Prioritizing Prevention

Report of the Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC)

FEBRUARY 2013

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About the IBCERCC

To reduce the burden of breast cancer on women and men of all ethnic groups, Congress passed Public Law 110-354, the Breast Cancer and Environmental Research Act, in 2008. The Act required the Secretary of the HHS to establish the IBCERCC.

The IBCERCC was charged with:

Reviewing federal research efforts concerning the environmental and genomic factors related to breast cancer. Identifying scientific advances in breast cancer research and outlining key research questions, methodologies, and knowledge gaps.

Developing a comprehensive strategy for accelerating transdisciplinary, innovative, and collaborative research on breast cancer and the environment across federal agencies and in partnership with nonfederal organizations.

Determining how to increase public participation in decisions about breast cancer research and the optimal mode of dissemination of information on research progress.

The Committee, supported by staff from the NIEHS and NCI, was comprised of federal members from agencies involved in research on breast cancer and the environment including the NIEHS, NCI, EPA, the DoD, and the CDC; non-federal members from scientific and clinical communities; and non-federal members who represent individuals with breast cancer.

Disclaimer

The views expressed in this report are those of the authors and may not reflect the official policy or position of the Centers for Disease Control and Prevention, the Department of the Army, Department of Defense, the National Institutes of Health, the United States Environmental Protection Agency, or the United States Government.

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The Committee also would like to acknowledge the staff from both the NIEHS and the NCI who dedicated considerable time and expertise as they provided ongoing consultation during Committee deliberations and/or drafted and edited portions of this report. In particular, the following staff members put in long hours throughout many months to help with the report's development: Gary Ellison, Chinonye Harvey, Christie Kaefer, Edward Kang, and Laura McGuinn.

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CHAPTER 1

Executive Summary

Breast cancer takes a tremendous toll on women and men of all ages, races, and ethnicities, as well as on their families and communities. Breast cancer also has a huge impact on the health care system that treats and monitors those people who have been diagnosed with the disease and provides end-of-life care for those who die from it. Prevention is the key to reducing the emotional, physical, and financial burden of breast cancer. Despite decades of productive breast cancer research, the number of women diagnosed with the disease continues to rise. In 2012, an estimated 227,000 women and 2,200 men in the United States will be diagnosed with breast cancer, and approximately 40,000 women will die from it.[1] Worldwide, breast cancer is the most commonly diagnosed malignancy and the leading cause of cancer death in women, accounting for approximately 14 percent of cancer deaths.[2, 3]

Researchers have long known that genetic and environmental factors individually contribute and interact with each other to increase breast cancer risk. Studies show that breast cancer rates can vary with changing environmental circumstances. Furthermore, the large majority of cases occur in women with no family history of breast cancer. Environmental factors are more readily identified and modified than genetic factors and therefore present a tremendous opportunity to prevent breast cancer.

On October 8, 2008, Congress passed the Breast Cancer and Environmental Research Act.[a] The Act required the Secretary of the U.S. Department of Health and Human Services (HHS) to establish an Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC) of federal and nonfederal members to examine the current state of breast cancer and the environment research and make recommendations for eliminating any knowledge gaps in this area.

Prevention is the key to reducing the burden of breast cancer.

The large and increasing burden of breast cancer demands innovative research and bold new approaches to uncover the intricate combination of factors inside and outside the body that lead to the disease. Based on our review of the state of the science, current programs and investments by federal agencies and nongovernmental organizations, and relevant communication efforts and policies, the IBCERCC offers seven recommendations to highlight the urgent need for coordinated, targeted efforts to identify and mitigate the environmental causes of breast cancer.

[a] Breast Cancer and Environmental Research Act of 2008, P. L. No. 110-354, 122 Stat. 3984 (October 8, 2008). http://www.gpo.gov/fdsys/pkg/PLAW-110publ354/pdf/PLAW-110publ354.pdf

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Committee Recommendations

- Prioritize prevention.
- Transform how research is conducted.
- Intensify the study of chemical and physical factors.
- Plan strategically across federal agencies.
- Engage public stakeholders.
- Train transdisciplinary researchers.
- Translate and communicate science to society.

By urgently pursuing research, research translation, and communication on the role of the environment in breast cancer, we have the potential to prevent a substantial number of new cases of this disease in the 21st century.

What is the environment?

For this report, the environment includes:

- **Lifestyle and behavioral factors**, such as alcohol intake and physical activity.
- **Chemical** agents that people are exposed to through pesticides, industrial pollutants, consumer products, and medications.
- **Physical** agents, such as radiation from medical and other environmental sources and other nonchemical substances.
- **Social and cultural influences**, such as family, community, psychosocial/social, and societal factors that may influence breast cancer risk.

Prioritize Prevention

The Committee recommends a national breast cancer prevention strategy to prioritize and increase federal government investments in breast cancer prevention.

Historically, investments in breast cancer research have focused primarily on diagnosis and cure. Comparatively speaking, there are remarkably few examples of advances in the area of breast cancer prevention, and finding ways to identify and mitigate the environmental causes of the disease has not been a priority. At the federal level, only a small number of efforts target breast cancer and the environment. The Committee notes that, at most, 10 to 11 percent of breast cancer research projects funded by the National Institutes of Health (NIH) and the U.S. Department of Defense (DoD) focus on environmental health. No other federal agency supports substantial research on the environmental causes of breast cancer. Other federal agencies and nongovernmental organizations, however, support and conduct research related to breast cancer and the environment and are important partners in any effort to prevent breast cancer.

Breast cancer prevention is underfunded at the federal level in both research and public health programs, and future investments must focus on this area. Enhanced investments would facilitate sustained coordination across research and regulatory agencies with the objective of reducing or eliminating harmful environmental exposures and modifying social and lifestyle factors implicated in breast cancer.

Transform How Research Is Conducted

The Committee recommends investigation into compelling scientific themes using a transdisciplinary approach.

Studies of breast cancer over time have revealed a complex disease. Researchers have distinguished several subtypes of breast cancer, each with potentially different causes and contributing factors that could require different approaches for research and for prevention.[4] By engaging investigators from many disciplines, including epidemiology, basic/mechanistic science, toxicology, social science, and computer and information science, new ways of thinking about breast cancer prevention can be developed. Investing in the development of tools to facilitate knowledge management and integration also is essential for success.

Factors such as lifestyle, social context, economic determinants, and disproportionate environmental exposures must be examined, particularly in minority and underprivileged populations. In addition, studies must examine how exposures and risk profiles differ among racial and ethnic groups, particularly groups that are insufficiently studied. Targeted research can improve understanding of the specific environmental risks for breast cancer in underserved populations. This research can in turn form the basis for new, comprehensive policies to reduce the broad spectrum of exposures that increase risk, ameliorate environmental disparities, and promote behaviors that can reduce breast cancer risk.

The complexity of breast cancer necessitates increased investment in research to explore compelling themes, such as mechanisms underlying breast cancer subtypes and breast density, epigenetic alterations (heritable changes that do not involve changes in DNA sequences) that occur over the life course, and gene/environment interactions. Specific exploration of the impact of environmental factors on breast development also is needed because altered development may influence breast cancer risk. In addition, research must evaluate the impact of multiple risk factors and periods when the breast may be most susceptible to exposures. Finally, research is needed to explore how people understand environmental risk issues.

Accelerating the research process will require fully utilizing high-throughput technologies that are capable of evaluating multiple potential risk factors simultaneously. Streamlined study protocols also are needed to enable scientists to quickly understand the potential of particular risk factors and environmental agents that cause breast cancer and conduct studies to test their hypotheses. In addition, rapidly deployable research funding mechanisms and resources are needed to address emerging issues related to breast cancer and the environment. Excellent examples of these types of mechanisms and resources exist, but could be enhanced and more fully deployed.

Intensify the Study of Chemical and Physical Factors

The Committee recommends research on the effects of chemical and physical factors that potentially influence the risk of developing and likelihood of surviving breast cancer.

Past studies have identified contributors to breast cancer risk, including: (1) increased age; (2) family history of breast cancer; (3) certain rare genetic variants, including BRCA 1 and 2; (4) alcohol consumption; (5) a sedentary lifestyle; (6) benign breast disease; (7) high breast density; (8) radiation exposure; (9) a number of reproductive characteristics, including early age at menarche; (10) hormonal influences; and (11) high body mass index for risk of postmenopausal breast cancer. These recognized risk factors have not been examined in interaction with physical and chemical exposures, and most have not been examined by breast cancer subtype.

In addition to these established risk contributors, several other risk factors have been identified with some evidence linking them to breast cancer. The Committee recommends making research efforts to close the knowledge gap about these potential risk factors a priority. Characterizing the myriad of exposures in our environment is another important challenge. Certain chemicals—for example, endocrine disruptors and physical agents such as low-dose radiation—require further research that employs the animal-human paradigm. This paradigm integrates animal and human research to accelerate progress in understanding breast cancer. Filling knowledge gaps regarding how environmental exposures affect the mammary gland in animals and the breast in humans requires a comprehensive approach that includes *in vivo, in vitro*, and human studies.

Improved understanding of the molecular and clinical features of the different subtypes of breast cancer, the availability of high-throughput testing methods, and the integration of different types of chemical testing have created opportunities to make

rapid progress in understanding breast cancer and the environment. These recent innovations, in addition to the study of biological mechanisms such as epigenetics, may help to explain how environmental factors influence breast cancer risk. We need to know how and when environmental exposures, singly and in mixtures, influence breast cancer risk and how this risk may vary at different exposure levels or doses.

Plan Strategically Across Federal Agencies

The Committee recommends that federal, state, and nongovernmental organizations coordinate and collaborate to accelerate the pace of scientific research on breast cancer and the environment.

Federal research into breast cancer is a blend of studies conducted by government scientists and research supported by targeted grant and contract programs based on agency priorities or investigator-initiated grants. A limited number of federally directed research programs and investigator-initiated projects focus specifically on breast cancer and the environment. To close this critical gap, the Committee recommends that, as part of a national breast cancer prevention strategy (see recommendation 1), federal agencies plan strategically for breast cancer and the environment research to be developed across the government to foster innovation and collaborative science. Joint planning and better coordination of the efforts of both governmental and nongovernmental funding agencies would increase the visibility of research on breast cancer and the environment, promote the goal of breast cancer prevention, facilitate sharing of resources (e.g., funding, data, research tools), help identify the most critical scientific questions, and facilitate the monitoring of progress toward answering these questions. In implementing a federal breast cancer and the environment research strategy, the Committee sees the need for comprehensive research management tools to help conceptualize and guide planning and prioritization of future federal programs as well as efforts to expand interagency collaborations and public-private partnerships.

Engage Public Stakeholders

The Committee recommends that the research planning, implementation, and translation process include stakeholders who represent the public and affected communities at every stage.

Advocates and community organizations have long played a direct role in establishing priorities for breast cancer research, securing funding, conducting and overseeing federally funded research, and disseminating and translating research information to patients and the general population. In addition, advocates have played an important role in the design and implementation of many studies focusing on breast cancer and the environment.

Public representatives should be involved as partners in the design and implementation of research programs to ensure that the research addresses public needs and interests. Public representatives also are critical to ensuring that research findings are translated into public health and regulatory actions and in communicating research and intervention needs to a diverse public. Furthermore, as agencies develop and apply standards for testing the effects of chemical and physical exposures, public participation can provide information about the exposures of greatest concern to the general public and specific communities.

To ensure effective translation and dissemination of breast cancer research findings as the field progresses, active participation of breast cancer advocates, community representatives, and members of the public in research planning and prioritization must increase. These stakeholders provide unique perspectives and expertise on research priorities, optimal modes of public engagement, and best practices for translating and disseminating research findings to the public.

Train Transdisciplinary Researchers

The Committee recommends federal programs that encourage and enable scientists to engage in transdisciplinary research.

Accelerating research on breast cancer and the environment will require increasing the numbers of large, transdisciplinary activities. Scientists from many disciplines must be engaged to develop new ways of thinking about breast cancer prevention. Scientists require training across the career trajectory—from undergraduate to investigator—to develop the skill sets necessary for active and effective engagement in transdisciplinary research. Opportunities and incentives for acquiring these skills are needed to promote involvement.

Currently, opportunities for scientists to learn how to function in a transdisciplinary environment are limited. The National Institute of Environmental Health Sciences (NIEHS)/National Cancer Institute (NCI) Breast Cancer and the Environment Research Program (BCERP) is a model of transdisciplinary research and includes basic and population scientists, advocates, and community stakeholders. An example of collaboration across agencies is the National Toxicology Program (NTP), which coordinates toxicology testing programs across the federal government and involves NIEHS, the Centers for Disease Control and Prevention (CDC), and the U.S. Food and Drug Administration (FDA). The NTP Executive Committee also includes the NCI, U.S. Environmental Protection Agency (EPA), DoD, Consumer Product Safety Commission, and Occupational Safety and Health Administration (OSHA).

Translate and Communicate Science to Society

The Committee recommends that the translation and dissemination of research findings be built from the start into every funded program that focuses on breast cancer and the environment.

Primary prevention of new breast cancer cases requires a focus on identifying and reducing exposures that increase the risk of the disease and fostering behaviors that may help to prevent it. As science improves understanding of the causes of breast cancer, research findings must be translated into clinical and educational interventions and policies that support prevention. These translation activities require that accessible information reach stakeholders from multiple audiences. It is critical that advocates and other community stakeholders participate in the research translation process to interpret and communicate findings to diverse audiences in ways that facilitate their application to public concerns. Translation of research findings also can be accelerated through use of evidence-based practices that promote the integration of research findings and evidence into health care policy and practice. Continued investment in implementation science will help to generate evidence on best practices for research translation and dissemination. Routinely including culturally appropriate targeted dissemination and communication efforts in funded projects from their outset will help to ensure that science enters the public domain rapidly and accurately and reaches stakeholders who are invested in breast cancer prevention. Research is needed to determine the best dissemination and communication approaches to achieve this goal. Translation, dissemination, and communication of research findings must proactively protect public health and guide the advancement of regulatory policies that create measurable changes in environmental factors linked to breast cancer incidence, morbidity, and mortality.

Conclusion

Prevention is the key to reducing the burden of breast cancer.

Science must seek greater understanding of the environmental and genetic factors that influence risk, susceptibility, and the progression of the disease, in addition to searching for new diagnostic tools and cures. Enhanced investment in prevention

research—from the initial concept of studies built on strong partnerships between breast cancer advocates and scientists to the timely dissemination and translation of research findings—ultimately will reduce the incidence of breast cancer in future generations.

The Committee submits these recommendations to the Secretary of the HHS with a vision toward reducing or eliminating environmental exposures and modifying social and lifestyle factors implicated in breast cancer. The Committee acknowledges that there are many points of view regarding the path forward to a breast cancer prevention strategy. Prevention does not come easily. The issues must be discussed widely, broadly, often, and vigorously to inform science, public health practice, and policy. Sustained coordination across research and regulatory agencies as well as nongovernmental organizations will be necessary to achieve our vision.

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CHAPTER 2

Introduction

Breast cancer is a complex disease that affects women and men of all ages and ethnic groups. Despite decades of productive research on breast cancer diagnosis and treatment, preventing this cancer is the only way to reduce the human toll of this disease that affects 1 in 8 women in their lifetime.[1] In 2012, an estimated 227,000 women and 2,200 men in the United States will be diagnosed with breast cancer, while approximately 40,000 women will die from it.[2] The huge burden of disease demonstrated by these numbers suggests the need for creative and innovative research and bold new approaches to uncover the intricate combination of factors, both within and outside of the body, that lead to breast cancer.

The term "breast cancer" encompasses more than one disease; it is an umbrella term for several subtypes of cancer of the breast. These breast cancer subtypes differ in their clinical presentation, reveal distinct gene expression patterns, and have different genetic and molecular characteristics.[3-5] The different breast cancer subtypes may have some shared as well as unique causes and contributing factors that might influence approaches to prevention.[6]

The strong relationship between breast cancer risk and a family history of breast cancer indicates that genetic factors play an important role in the disease.[7] Most breast cancers, however, occur in people with no family history,[8] so environmental factors—broadly defined—must play a major role in the etiology of the disease. Yet, preventing breast cancer by finding ways to identify and influence environmental causes of the disease has proven to be extremely challenging and has not been a priority. To identify the environmental causes of breast cancer, we must expand our knowledge about normal breast development, including changes in the breast in childhood and adolescence, and about the way that stressors in the environment alter normal breast development and influence risk for cancer, risk of a new cancer developing in the second breast, and risk of death from breast cancer. We also must expand our knowledge about interventions that could effectively reduce the impact of known risk factors for breast cancer. Many known risk factors, such as age at first menstrual period,[10] cannot be easily altered to prevent this disease. Substantial evidence from randomized, controlled trials and translation research in the community, however, indicates that known, modifiable risk factors for breast cancer can be changed (i.e., increasing physical activity and

We urgently need to accelerate progress toward understanding the role of the environment in breast cancer prevention. Primary, secondary, and tertiary prevention all must be considered. Primary prevention is directed at stopping the onset of a targeted condition. Secondary prevention identifies and treats asymptomatic persons who already have developed risk factors or preclinical disease but in whom the condition has not become clinically apparent. Tertiary prevention refers to the treatment and management of persons with clinical disease.[9]

reducing weight) using cost efficient approaches.[11,12] Behavioral interventions targeting weight loss and physical activity at the individual level have shown that it is difficult for participants to maintain weight and recommended health habits. Interventions at the community, state, and national levels, such as policy changes, will be needed to achieve lasting improvements in weight and physical activity in target populations.[13] In addition, medications such as tamoxifen, which can reduce the incidence of breast cancer in women at high risk of the disease, have serious side effects.[14] Many women who might benefit from tamoxifen in terms of breast cancer prevention do not take this medication, in part because of these side effects.[15]

In spite of many unknowns and substantial obstacles to progress in understanding the environmental contributors to breast cancer, scientists are finding important clues about how the disease develops and identifying new opportunities that could lead to breakthroughs in the prevention of this complex disease. For example, investigators are learning that the timing of a person's exposure to certain environmental factors influences breast cancer risk, and that some environmental factors affect survival from the disease. New and improved technologies to assess exposures to the mixtures of environmental contaminants and potential carcinogens at home, in the workplace, and in our communities,[16] as well as new approaches to monitoring lifestyle factors,[17] are creating unprecedented opportunities to advance breast cancer prevention research. At the same time, basic laboratory research is rapidly uncovering underlying biological mechanisms of cancer causation,[18] presenting the opportunity to examine how the reduction or elimination of exposures will help prevent breast cancer. Transdisciplinary research will accelerate progress towards understanding breast cancer and the environment, which ultimately will affect public health. Now is the time to accelerate progress toward understanding the role of the environment in breast cancer prevention.

2.1 Legislation/Congressional Charge to This Committee

In 2008, Congress passed Public Law (P.L.) 110-354, the Breast Cancer and Environmental Research Act.[a] P.L. 110-354 required the Secretary of the U.S. Department of Health and Human Services (HHS) to establish an Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC). The Committee mandate was to review research conducted or supported by federal agencies on environmental exposures that could influence breast cancer risk and make recommendations for innovative research strategies and opportunities to understand the role of these exposures and other factors in the context of inherent biological determinants of the disease. The Committee's ultimate goal is to recommend research that will provide the evidence to inform, enable, and promote breast cancer intervention programs across the cancer control continuum—from prevention through detection, diagnosis, treatment, and survivorship—to reduce the burden of breast cancer.

The Committee's ultimate goal is to recommend research that will provide the evidence to inform, enable, and promote breast cancer intervention programs across the cancer control continuum—from prevention through detection, diagnosis, treatment, and survivorship—to reduce the burden of breast cancer.

The duties of the Committee, as set forth in the authorizing legislation, are to:

- Share and coordinate information on existing research activities and make recommendations to the National Institutes of Health (NIH, part of HHS) and other federal agencies regarding ways

[a] Breast Cancer and Environmental Research Act of 2008, P. L. No. 110-354, 122 Stat. 3984 (October 8, 2008). Available from: http://www.gpo.gov/fdsys/pkg/PLAW-110publ354/pdf/PLAW-110publ354.pdf.

- to improve existing research programs that are related to breast cancer.

- Develop a comprehensive strategy and advise the NIH and other federal agencies on the solicitation of proposals for collaborative, transdisciplinary research, including proposals to evaluate environmental and genomic factors that may be related to the etiology (or causes and origins) of breast cancer that would:
  - » Result in innovative approaches to studying emerging scientific opportunities or eliminating knowledge gaps and thereby improve the research portfolio.
  - » Outline key research questions, methodologies, and knowledge gaps.
  - » Expand the number of research proposals involving collaboration between two or more national research institutes or national centers (including proposals for the NIH Common Fund) and;
  - » Increase the number of collaborative, transdisciplinary, and multi-institutional research grants.

- Develop a summary of advances in breast cancer research supported or conducted by federal agencies relevant to the diagnosis, prevention, and treatment of cancer and other diseases and disorders.

- Make recommendations to the Secretary of HHS about:
  - » Changes to research activities, including recommendations to improve the research portfolio of the NIH and ensure that scientifically based strategic planning is implemented in support of priorities that affect breast cancer research activities.
  - » Enhanced cooperation across the activities of the NIH and other federal agencies, including the U.S. Department of Defense (DoD), thereby reducing duplication of effort.
  - » Public participation in decisions about breast cancer research, to increase the involvement of patient advocacy and community organizations that represent a broad geographical area.

Congress asked the Committee to:

- Identify advances related to breast cancer and the environment and key scientific questions to answer.
- Propose ways to improve the research process and engage the public in this process and the dissemination of findings.
  - » The optimal mode of dissemination of information on breast cancer research progress.
  - » Strategies to expand partnerships between public entities and federal agencies and private entities to enhance collaborative, cross-cutting research.

Under P.L. 110-354, IBCERCC comprised:

- Federal members, including representatives from the Centers for Disease Control and Prevention (CDC), the National Institute of Environmental Health Sciences (NIEHS), the National Cancer Institute (NCI), the NCI Board of Scientific Advisors (BSA), other HHS agencies as the Secretary deems appropriate, and other federal agencies that conduct or support cancer research, including the DoD.

- Nonfederal members from (a) the scientific or medical communities who represent multiple disciplines and different geographical regions of the country; and (b) practice settings, academia, or other research settings. These members included individuals experienced in the scientific peer-review process.

- Nonfederal members who represent individuals with breast cancer.

- As many nonvoting members as the Secretary deemed appropriate.

In June 2009, the Secretary of the HHS, Kathleen Sebelius, delegated the authority for implementing IBCERCC to the NIH. The Director of the NIH delegated this task specifically to the NIEHS in July 2009. The Charter for the Committee was signed by the Director of NIEHS, Dr. Linda Birnbaum, on September 3, 2009 (see Appendix 1).

NIEHS and NCI staff organized the Committee under the rules for NIH Federal Advisory Committees.[19] Formal meetings of the full Committee took place on September 30 to October 1, 2010, in Washington, DC; on May 12 to 13, 2011, September 26 to 27, 2011, and January 23 to 24, 2012, at NIEHS in Research Triangle Park, NC; and on May 9, 2012, in Arlington, VA. In addition to formal meetings, members used email, teleconferences, and informal meetings to jointly accomplish the activities required of the Committee. To complete the work, the Committee worked principally through three subcommittees on the state of the science; research process; and translation, dissemination, and policy implications. Each subcommittee included clinicians, scientists, advocates, and community members, and all Committee members interacted extensively during the preparation of this report.

The report has been written jointly by scientists, government agency representatives, clinicians, advocates, and consumer representatives.

At the initial meeting of the Committee, Dr. Birnbaum asked the IBCERCC "to address the legislative mandate boldly and provocatively, consider the totality of the issues before prioritizing them, and develop a usable product that will guide the future of federally conducted and supported research on breast cancer and the environment."

2.2 Defining the Environment

For the purposes of this report, the environment includes all of the surroundings of and influences on living organisms. The types of environmental factors discussed in this report are:

- Lifestyle and behavioral factors such as alcohol intake, physical activity, weight gain in adulthood, and night shift work.
- Chemical substances to which people are exposed through pesticides, industrial pollutants, consumer products, and medications.

The environment includes lifestyle and behavioral factors, chemical and physical agents, and social and cultural influences.

- Physical factors such as radiation from medical and other sources, light at night, and other non-chemical exposures.
- Social and cultural influences, such as family, community, psychosocial/social, and societal factors that determine exposure to; the extent of exposure to; or ability to ameliorate the impact of chemical, physical, lifestyle, and behavioral factors that influence breast cancer risk.

People may be exposed to mixtures or combinations of these factors, which may interact with each other and/or with genetic or other breast cancer susceptibility factors to increase or decrease breast cancer risk. Risk factors can be modified at the individual level (e.g., by changing personal behaviors) and/or the population level (e.g., by reducing or eliminating exposures received by groups of people). The next section discusses ways that the study of these factors could lead to approaches for preventing breast cancer.

2.3 Preventing Breast Cancer

Evidence suggests that breast cancer has the potential to be prevented. In addition to the fact that the majority of cases occur in women with no family history of the disease, the fact that breast cancer

rates change in response to certain environmental factors strongly supports the role of modifiable (non-genetic) factors in breast cancer risk. For example, a twin study in a cohort of 10,000 women demonstrated that only 27 percent of breast cancer risk was attributable to heritable factors, leaving much to be explained by environmental influences.[20] Studies of women who migrated from Asian countries to the United States showed that breast cancer rates in the migrant populations increased to become closer to those in the United States when migration occurred at younger ages[21] and with increased time in the United States.[22] The study by Ziegler and colleagues also found that women's breast cancer risk increased with a greater number of grandparents born in the West. In addition, parts of the world that are developing or in transition (such as northern Africa) have sharply escalating breast cancer rates.[23]

Approaches for preventing cancer include reducing exposure to agents that increase risk, sustaining a healthy lifestyle, and reducing susceptibility. One example of a change in individual behavior (by patients and physicians) that led to reduced breast cancer risk relates to the use of postmenopausal combined hormone therapy (HT). Although breast cancer incidence increased during the 1980s and 1990s, incidence data from 2002 to 2003 indicated a significant decline in breast cancer diagnosis in women in the United States.[24] The most common explanation for this decline is the sharp drop in the use of HT after the 2002 publication of the Women's Health Initiative findings that linked combined estrogen plus progestin HT with increased breast cancer risk.[24] Medical interventions that reduce susceptibility to breast cancer include tamoxifen and raloxifene, both of which have been shown in clinical trials to be effective in reducing breast cancer among women at high risk for the disease.[7] For women at extremely high risk of breast cancer, such as those with BRCA1 and BRCA2 genetic mutations, surgical interventions such as bilateral mastectomy (removal of both breasts) and/or oophorectomy (removal of ovaries)[25, 26] substantially reduce breast cancer susceptibility.

2.4 Concepts Considered Throughout the Report

The Committee considered the following key concepts in developing this report:

- **Leverage scientific advances across a wide range of disciplines and look for opportunities for collaboration to transform breast cancer science.** The Committee reviewed scientific research and training programs as well as the full spectrum of methods and disciplines that pertain to breast cancer and environment research. The Committee found gaps and opportunities in all areas, and the report is comprehensive in presenting these gaps/opportunities for consideration.

- **Recognize that the timing of exposure to environmental and lifestyle risk factors matters.** The molecular and cellular changes that lead to breast cancer can occur early in life and endure across the life span.[27] Susceptibility to the initiation of breast cancer changes begins with the developmental stage of the mammary gland (this report uses this term instead of "breast" when referring to laboratory animals) and continues through the many stages of mammary gland/breast development across the life span.[27] This Committee examined exposures throughout life, including intermediate markers of "risk" that influence breast pubertal development and age at menarche. The report also discusses "windows of susceptibility" during the life course when specific exposure(s) might have their greatest influence on lifetime breast cancer risk (e.g., *in utero*, puberty).

- **Forge partnerships with a variety of stakeholders.** Many voices are needed in the breast cancer and environment discussion, including the voices of federal and nonfederal research funders, researchers, advocates, policymakers, communication professionals, environmental health specialists, and health care providers. This report examines the current ways in which these diverse groups interact and develop strategies for enhancing the exchange of ideas, practices, and intervention

- approaches to stimulate and translate research on breast cancer and the environment. This report emphasizes the important roles of stakeholder groups and formulates strategies to engage these groups optimally in all research activities, from planning through knowledge integration and dissemination.

2.5 IBCERCC and Related Reports

The IBCERCC and two other authoritative reports focus on the environment and breast cancer or all cancers. One report was developed by the Institute of Medicine (IOM)[28] and the other, which focused on all cancers, was generated by the President's Cancer Panel.[b] In developing the reports, all of the committees/panels had mechanisms for obtaining public input and comment. The IBCERCC held open meetings and published a request for input in the Federal Register. The IOM committee held a meeting at which the members could listen to concerns of advocates and community members; the President's Cancer Panel held four town hall meetings in different regions of the United States in which anyone could participate.

Whereas the IOM and President's Cancer Panel reports focused on environmental influences on cancer, a third initiative, the National Conversation on Public Health and Chemical Exposures, addressed the effects of chemical exposures on environmental health more broadly. In that initiative, the CDC and the Agency for Toxic Substances and Disease Registry (ATSDR) engaged a broad range of stakeholders in the development of an action plan to protect the public from harmful chemicals.[29]

2.5.1 IOM Report

The IOM was commissioned by the Susan G. Komen for the Cure Foundation to review the criteria for identifying and measuring cancer risk factors, the strength of the science regarding the relationship between breast cancer and the environment, and potential interactions between genetic and environmental risk factors. The IOM also was asked to identify evidence-based actions that women could take to reduce their risk of breast cancer. Through its review of studies in humans, the IOM identified methodological challenges in conducting research on breast cancer and the environment and developed recommendations for future research. The recommendations emphasized the times during the life course when exposures might have the greatest impact on breast cancer. Major conclusions of the IOM report were the need for additional research on the causes of and ways to prevent breast cancer, and the difficulty in determining the contribution of many environmental factors to breast cancer risk.[28]

The IOM report is similar to this report in several aspects. Both reports include a broad definition of the environment. Both reports also provide an extensive literature review, along with recommendations that highlight research opportunities and descriptions of the challenges that hamper human studies of environmental exposures and breast cancer risk. The IOM report differs from this report in that the IOM committee was required by the sponsor to include recommendations about steps that individuals could take to reduce their breast cancer risk and to assess the standards by which recognized risk factors are measured. Unlike this report, the IOM report did not focus on the evaluation of the research process in government and nongovernmental organizations or include an examination of the dissemination and translation of research to the public.

2.5.2 President's Cancer Panel

The President's Cancer Panel is required under the National Cancer Act of 1971 to regularly appraise the National Cancer Program. In 2009 and 2010, the Panel assessed the state of research, policy, and programs and focused on known and potential effects of environmental exposures on cancer. The Panel examined key regulatory, political, industrial, and cultural barriers to understanding and reducing environmental and occupational carcinogenic

[b] http://deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp08-09rpt/PCP_Report_08-09_508.pdf

exposures and developed recommendations to mitigate or eliminate those barriers. The Panel's report considered industrial, occupational, and agricultural exposures as well as exposures related to medical practice, military activities, lifestyle (behaviors and practices that influence exposures to chemical and physical factors), and natural exposures.

The Panel's report concluded that the burden of cancer from environmental factors was underestimated and that there were many actions that industry, regulators, the public, and others could take to mitigate cancer risk from these environmental sources.[30]

The President's Cancer Panel report is similar to this report in that it includes a review of the state of the science and formulates recommendations for both research and research agencies. The Panel report differs from this report in that it discussed all cancers rather than concentrating specifically on an in-depth evaluation of the environment and breast cancer. The 2009–2010 President's Cancer Panel report also took a more limited view of lifestyle factors, discussing only those behaviors that are thought to influence exposure to chemical and physical agents. The IBCERCC report examines research on a broad array of lifestyle factors. In addition, the IBCERCC report considers the sociocultural experience as part of environment whereas the 2009–2010 Panel report did not. It is relevant to note that two other reports by the President's Cancer Panel included a broader discussion of lifestyle and sociocultural factors for all cancers.

2.5.3 National Conversation on Public Health and Chemical Exposures

In 2009, the National Conversation on Public Health and Chemical Exposures convened a leadership council and six working groups with highly diverse membership. Each working group prepared a report on a specific topic, including: (1) Monitoring, (2) Scientific Understanding, (3) Policies and Practices, (4) Chemical Emergencies, (5) Serving Communities, and (6) Education and Communication. In addition, 52 community forums were held across the nation, involving more than 1,000 people. Through the working groups and public forums, recommendations were formulated for monitoring and protecting the public from harmful chemicals and for strengthening the public's ability to participate effectively in environmental health decision making.[29] The process used for the National Conversation was unique in the highly participatory approach used to engage and obtain input from a large and diverse group of stakeholders, including members of the general public. This approach can serve as a model for other national environmental health initiatives.[31]

2.5.4 IBCERCC Report

This IBCERCC report differs from the earlier reports in that its charge focuses on ways the federal government can create new and innovative means to support research on the environmental causes of breast cancer. Chapter 3 provides information about the burden of breast cancer in the United States and the world. Chapter 4 provides a summary of major advances in breast cancer prevention, diagnosis, and treatment. Chapters 5 and 6 describe the state of the science related to breast cancer and the environment. These two chapters include a review of the scientific literature, an analysis of the scientific gaps and opportunities, and identify the most pressing scientific questions that need to be answered. The Committee applies an animal-to-human approach in the review of evidence and in formulating recommendations by discussing ways that animal models can provide insights into human breast cancer development and the role of the environment in breast cancer etiology. Throughout the report, the Committee considers a transdisciplinary approach to research as the ideal, and this perspective informs our recommendations. A transdisciplinary approach is based on researchers working together, using a shared conceptual framework, and combining discipline-specific theories, concepts, and methods to address a common problem.[32] The animal-to-human approach is described in greater detail in Chapter 5. The transdisciplinary approach is described in more detail in Chapter 6. Chapter 7 provides an analysis of federal and nonfederal organization

funding portfolios. This chapter offers specific recommendations to improve the research funding process to increase innovative, interagency, multidisciplinary investigations of breast cancer and the environment. Chapter 8 examines the translation, dissemination, and communication of research on breast cancer and the environment. Chapter 9 concludes the report and presents overarching recommendations and strategies for achieving those recommendations. Policy implications relevant to scientific inquiry, the research funding process, and research communication are discussed throughout the report. Most importantly, the report recommends establishing breast cancer prevention research as a priority and identifies strategies for increasing studies of breast cancer etiology and prevention.

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CHAPTER 3

Breast Cancer Burden

3.1 Introduction

Breast cancer is the most common cancer in women, the second leading cause of cancer death in women after lung cancer in the United States,[1] and the leading cause of cancer death in women worldwide.[2] The disease takes a tremendous toll on the women and men who develop and live with it, on the health care system that treats these patients, and on the patients' family members and communities. This chapter describes the burden of breast cancer in the United States and globally and how it differentially affects segments of the U.S. population.

3.2 Incidence and Mortality

The National Cancer Institute (NCI), the American Cancer Society (ACS), the Centers for Disease Control and Prevention (CDC), and the North American Association of Central Cancer Registries (NAACCR) collaborate to produce statistics on the cancer burden in the United States. NCI's Surveillance, Epidemiology, and End Results Program (SEER) and CDC's National Program of Cancer Registries (NPCR) collect information needed to produce estimates of incidence, mortality, survival, prevalence, and the probability of developing cancer, among other statistics.[3, 4] Together, SEER and NPCR collect cancer data for the entire U.S. population.

Data collected by these surveillance systems indicate that approximately 227,000 new cases of invasive breast cancer and another 63,000 new *in situ* cases are expected to be diagnosed in U.S. women in 2012.[1] Invasive breast cancer means that malignant cells have spread outside the milk ducts or lobules and into normal tissue. *In situ,* or noninvasive breast cancer, stays within the milk ducts or milk lobules in the breast and the cancer cells have not grown into or invaded normal tissues within or beyond the breast.[5] The information in the rest of this chapter refers to invasive breast cancer. No estimate of the burden of breast cancer due to ductal carcinoma *in situ* (DCIS) is provided in this chapter.

227,000 women and 2,200 men will be diagnosed with breast cancer in 2012.[1]

Breast cancer is a rare condition in men and comprises less than 1 percent of all U.S. breast cancer diagnoses. Nevertheless, in the United States, approximately 2,200 men will be diagnosed with breast cancer in 2012.[6] The risk of breast cancer increases with age, and the majority of women are diagnosed in their postmenopausal years. Half of all female breast cancer patients, however, receive their breast cancer diagnosis by age 61, and approximately 12 percent are diagnosed at ages younger than 45.[7] Between 1980 and 1987, breast cancer incidence rates increased by 4 percent annually, leveled off, and then between 1994 and 1999, increased by 1.7 percent annually. New cases of breast cancer declined by 2.1 percent annually from 1999 to 2005, and were stable between 2005 and 2009.[7] The decline in breast cancer rates between

1999 and 2005 is thought to result from a decrease in the use of postmenopausal combined hormone therapy (HT) after the 2002 publication of the Women's Health Initiative findings linking combined estrogen plus progestin HT with increased breast cancer risk.[8]

Breast cancer accounts for approximately 14 percent of all cancer deaths in the United States.[6] Approximately 40,000 breast cancer deaths are expected to occur in 2012. Breast cancer mortality trends reveal a drop in death rates, currently by 1.9 percent from 1990 to 2009, with a larger decline among women under the age of 50 compared with women of ages 50 and older.[7] These decreases in mortality are thought to result from treatment advances and earlier detection through screening.[9] Death rates for male breast cancer have decreased at an average rate of 2.3 percent per year since 2000.[6] In 2012, approximately 410 men will die from breast cancer.[6] Statistics cited in the rest of this chapter refer to women only because of the disproportionate impact of breast cancer on women.

3.3 How Breast Cancer Is Classified

Breast cancers can be classified in many different ways and for different purposes. Considerations include understanding how the disease develops, the tissues involved (e.g., whether it originated in the breast ducts that carry milk or the lobules), the prognosis, and treatment options. Classification systems have changed over time as more is learned about the biology and behavior of breast cancer. Major classification systems include: (1) an assessment by a pathologist examining tumor tissue that yields information about features, such as histologic cell type, extent of invasion into surrounding tissues, and indicators of aggressiveness; (2) staging, which classifies patients according to the size of the tumor and the extent of spread to nearby lymph nodes or other parts of the body; and (3) certain molecular markers found on or in tumor cells that influence prognosis (i.e., the likely outcome or course of a disease, including the chance of recovery or recurrence). The results of molecular marker tests are expressed as either positive "+" (having expression) or negative "–" (lacking expression). Some major molecular markers are based on whether a tumor has receptors (binding sites) for the hormones estrogen (estrogen receptor is abbreviated as ER) and progesterone (progesterone receptor is abbreviated as PR) or the protein HER2. Triple-negative breast cancers (TNBCs) are cancers in which the tumor does not express any of the three major molecular markers (ER, PR, or HER2). Other molecular markers have been identified that are based on the expression of other proteins (e.g., Ki-67, cytokeratin 5/6 [CK5/6]).[10] Five molecular subtypes of breast cancer have been identified that involve specific combinations of these markers that reflect distinct gene-expression patterns, including: (1) Luminal A; (2) Luminal B; (3) HER2+/ER–; (4) basal-like; and (5) unclassified.[10] Because these gene-expression patterns include, among other markers, ER, PR, and HER2, there is some overlap between the five molecular subtypes and classifications based on ER, PR, and HER2 only. Recent research suggests that additional breast cancer subtypes may exist.[11]

There are at least five different breast cancer subtypes—each with distinct biologic features, clinical outcomes, and responses to therapy.

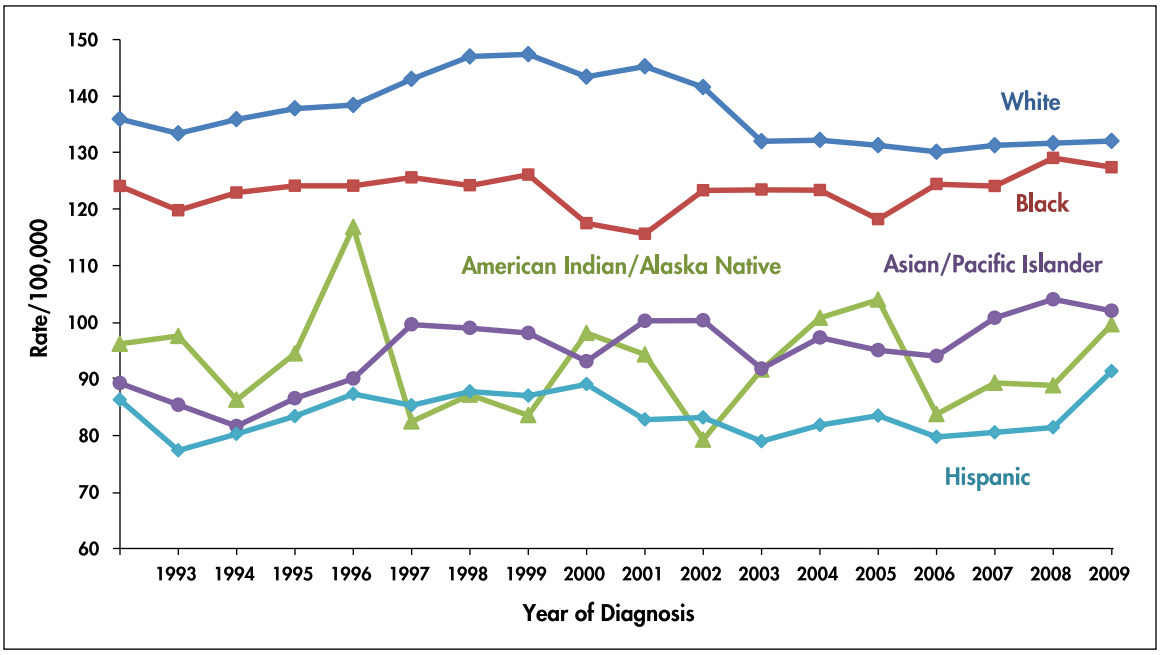
TNBC and basal-like breast cancer (TNBC with additional molecular characteristics) are particularly aggressive.[12] Women with basal-like, TNBC, and HER2+ tumors have a worse overall prognosis with shorter time to progression and lower overall survival compared to women with Luminal A or B tumors, which are ER+ and/or PR+.[13, 14] Another type of breast cancer that is not defined by molecular markers is inflammatory breast cancer (IBC). This type of breast cancer has a unique clinical and pathological presentation and has been hypothesized to have a different etiology from other forms of the disease.[15] IBC is considered a very aggressive form of breast cancer with rapid progression and poor survival.[16] Racial/ethnic differences in incidence and mortality have been found for these breast cancer types. These differences are discussed in Section 3.4.

A recent pooled analysis of epidemiologic studies of breast cancer subtypes[17] showed that higher body mass index (BMI) was associated with Luminal A tumors in postmenopausal women and suggested a higher TNBC risk in premenopausal obese women. Although evidence suggests that higher parity (having more children) reduces the risk of Luminal A breast cancer, recent studies found that higher parity also increased the risk of basal-like and ER– breast cancer.[18, 19] Breast cancer subtypes differ in prevalence by age, with basal-like breast tumors more common among younger women.[18] The different clinical, demographic, and risk factor profiles for breast cancer subtypes justify consideration of these subtypes as separate disease entities. Improved understanding of these subtypes is helping to explain some of the patterns of breast cancer and breast cancer disparities in population groups in the United States.

3.4 Breast Cancer Risk and Mortality Varies Significantly by Race and Ethnicity

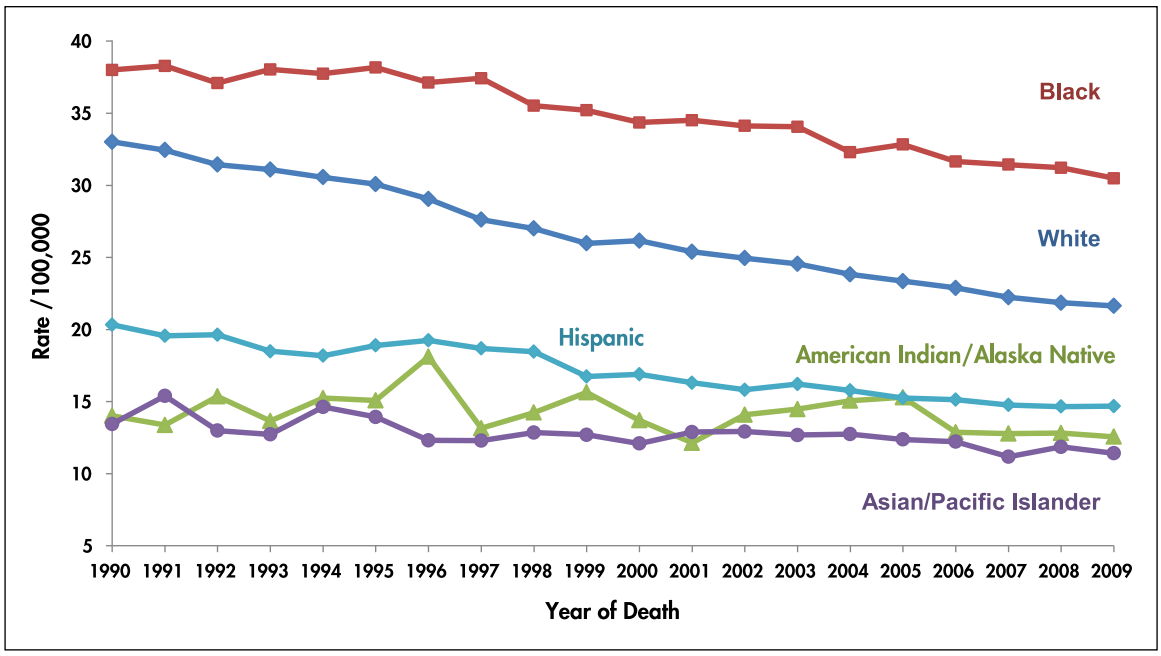
As shown in Figure 3.1, breast cancer incidence rates (the number of new cases of breast cancer per 100,000 women per year) are highest for White women, next highest for Black women, followed by Hispanic, Asian and Pacific Islander, and American Indian and Alaska Native women. Trends in breast cancer rates over time also vary by race and ethnicity.[7] Most recently, from 2000 to 2009, breast cancer incidence rates declined among White women but have been statistically stable for the other racial/ethnic groups (Figure 3.1). Breast cancer death rates are declining in all racial and ethnic groups over time (Figure 3.2). Black women experience

Figure 3.1. Female breast cancer incidence rates by race and ethnicity



This figure displays female breast cancer incidence rates in the United States for the years 1992 to 2009 for White, Black, American Indian and Alaska Native, Asian and Pacific Islanders, and Hispanic women. Hispanic refers to individuals who indicated Hispanic ethnicity regardless of racial group. From 2000 to 2009, breast cancer incidence rates declined among Whites, but have been statistically stable for the other racial/ethnic groups.[7] Rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population.[3] Data for White and African American women are from the original nine SEER registries and were adjusted for reporting delays. Data for other races/ethnicities are from the 13 SEER registries. For Hispanic women, incidence data do not include cases from the Alaska Native Registry. Incidence data for American Indians/Alaska Native women are based on Contract Health Service Delivery Area (CHSDA) counties.

Figure 3.2. Female breast cancer death rates by race and ethnicity



This figure displays female breast cancer death rates in the United States for the years 1990 to 2009 for White, Black, American Indian and Alaska Native, Asian and Pacific Islander, and Hispanic women. Hispanic refers to individuals who indicated Hispanic ethnicity regardless of racial group. Rates are per 100,000 persons and are age-adjusted to the 2000 United States standard population.[3] Information is included for all states except Connecticut, Louisiana, Maine, Maryland, Minnesota, Mississippi, New Hampshire, New York, North Dakota, Oklahoma, South Carolina, Vermont, and Virginia, and the District of Columbia.[3]

the highest death rate from breast cancer despite a lower incidence rate than White women, as shown in Figure 3.2. This disparity may be due to more aggressive tumor biology, later stage at diagnosis, and/or factors related to access to care and receipt of optimal treatment.[7, 20-23]

Current evidence indicates that Black women are more likely than non-Hispanic White or Hispanic women to be diagnosed with tumors that have more aggressive features in the pathological examination and molecular marker assessment, such as TNBC,[24]

We need to know why some aggressive forms of breast cancer are more common in Black women.

high-grade and TNBC,[20] and basal-like breast cancer.[25] Data from 2004 to 2007 also reveal that age-specific rates of IBC were higher for non-Hispanic Black women than for non-Hispanic White or Hispanic women.[15] In addition, Black women are more likely to be diagnosed before age 40[20] and with later stage breast cancer.[7] Hispanic and Native American women also are diagnosed with later stage breast cancer compared to White women, suggesting that late-stage diagnosis is, in part, associated with racial/ethnic minority status[23] and factors associated with that status, such as lower income and lack of health insurance.[21, 22] For example, studies have shown that, compared to non-Hispanic White women, other racial/ethnic groups may have less access to mammograms.[26, 27]

Mortality from breast cancer is higher in persons with lower socioeconomic status (SES)[28, 29] SES is an indicator for a constellation of other factors that potentially contribute to disparities in breast cancer, including availability and access to health care[30] and exposure to environmental contaminants of potential relevance to breast cancer, such as endocrine-disrupting chemicals.[8, 31, 32]

3.5 Survival, Recurrence, and Second Breast Cancers

Relative survival is a way of comparing the survival of people in the general population who have a specific disease with those who do not. The percentage of survivors is usually determined at specific times, such as 5 years after diagnosis or treatment. The relative survival rate shows whether the disease shortens life. Five-year relative survival from breast cancer is 90 percent for women diagnosed in the years 2002 to 2008. Survival, however, depends on the stage at diagnosis. Sixty percent of invasive breast cancers are localized (confined to the breast), 33 percent are regional, and 5 percent are metastatic when they are diagnosed. When cancer is confined to the breast, the 5-year relative survival is 98.4 percent. When breast cancer has metastasized (spread) to other organs, however, the 5-year relative survival is only 23.8 percent.[33]

Even if they survive for 5 years after diagnosis, breast cancer patients continue to be at risk of breast cancer recurrence and of developing cancer in the opposite breast.[34] Cancer recurrence is defined as cancer that has returned, usually after a period of time during which the cancer could not be detected. The cancer recurs because not all of the breast cancer cells present in the body were completely eradicated by the therapies used to treat the cancer. It may come back in the same place as the original breast tumor or to another place in the body to which it spread from the primary site. One national study of women with breast cancer diagnosed at ages 65 through 80 found that the cancer recurred in 36.8 percent of these cases over 10 years.[35] The rate of breast cancer recurrence varies by breast cancer subtype, stage at diagnosis of the first primary cancer, treatment, and the screening modality used to identify the recurrence.[36-38] Women with specific tumor subtypes, such as HER2+ and TNBC, are more likely to experience a recurrence.[39, 40]

Seven percent of breast cancer patients develop a second breast cancer, usually in the opposite breast.[41] Women with breast cancer have a 67 percent increased risk of a new breast cancer diagnosis during the first 10 years after the initial diagnosis compared to women in the general population.[41] Established risk factors for developing a second primary breast cancer suggest a genetic influence and include: (1) a family history of breast cancer;[42] (2) certain identified genetic characteristics;[43] (3) breast density;[42] and (4) early age at diagnosis.[42] Additional risk factors are related to the treatment for the first breast cancer and include (1) having breast-conserving surgery but no radiation therapy;[42] and (2) not having adjuvant treatment (a treatment in addition to the primary treatment).[44]

3.6 Survivorship

On January 1, 2008, there were 2.6 million female breast cancer survivors in the United States.[45] The estimated number is 3 million as of January 1, 2012.[46] Treatment for breast cancer has improved substantially over time in terms of the success of the treatment, the opportunities to tailor the treatments

Survivors experience physical and psychological consequences of the disease and require long-term medical monitoring.

to specific subtypes of cancer, control of symptoms resulting from treatment, and palliation of advanced breast cancer. Nevertheless, most breast cancer patients, even some diagnosed with early stage disease, must endure surgery, chemotherapy, radiation therapy, and multiyear courses of hormone therapy, each with attendant physical, psychological, and social costs.[a]

Survivors continue to experience the consequences of the disease years beyond the initial diagnosis. These consequences include risk of recurrence and new primary cancers, long-term physical and psychological effects of the treatment and disease

[a] http://www.cancer.gov/cancertopics/pdq/treatment/breast/healthprofessional/

and, for many survivors, long-term or life-long treatment and increased medical screening and monitoring.[47] Late physical effects of treatment are common and can include cardiotoxicity,[48] lymphedema,[49] and fertility concerns.[50] Psychological consequences of breast cancer can include psychosocial distress and depression.[51]

The most recent projected 2012 U.S. national cost of breast cancer was $17.35 billion.

The most recent projected 2012 national cost of cancer care for breast cancer was $17.35 billion.[52] These costs are only a small part of the overall social, economic, and medical burden of breast cancer. Despite declines in mortality, the economic value of life lost due to premature death from breast cancer is estimated to reach $121 billion by the year 2020.[53] Caregivers of breast cancer patients also are affected significantly by this disease, with substantial expenditures and time spent on providing care.[54]

3.7 Global Burden of Breast Cancer

Breast cancer is not only a U.S. problem. Globally, an estimated 1.38 million women were diagnosed with invasive breast cancer in 2008.[55] Worldwide, breast cancer is the most commonly diagnosed malignancy and the leading cause of cancer deaths in women, accounting for approximately 14 percent of cancer deaths in women.[2, 55]

Breast cancer is a global problem. Worldwide, breast cancer is the most commonly diagnosed malignancy and the leading cause of cancer deaths in women, accounting for approximately 14 percent of cancer deaths in women.

About half of new breast cancer cases occur in economically developed countries. Female breast cancer incidence rates have been declining since the late 1990s in the United States, Australia, the United Kingdom, and most other European countries, but continue to increase in many parts of the world. Incidence rates in Asia and Africa have seen dramatic increases in recent years, which have been attributed to changes in reproductive patterns, increased obesity, decreased physical activity, and limited increases in screening rates. Mortality from breast cancer in most of the developed countries has remained stable or decreased slightly during the past 25 years, primarily due to earlier detection and improvements in treatments. Breast cancer death rates continue to increase in the rest of the world, probably due to the increased incidence of breast cancer in developing countries.[55] The percent of women surviving breast cancer ranges from 73 percent in all developed countries, with a high of 81 percent in the United States, to 57 percent in all developing areas, with a low of 32 percent in Sub-Saharan Africa.[56]

3.8 The Importance of Surveillance in Monitoring the Cancer Burden

The United States has a nationwide cancer surveillance system and several other surveillance systems that that collect demographic, health behavior, and other data needed to measure the cancer burden and identify factors that may affect that burden. These surveillance systems are described in Chapter 7. Research on breast cancer and the environment would benefit from a national cancer surveillance system that provides more detail about cancer subtypes and is linked to more sociodemographic, economic, environmental, and geographic data. A major gap in the U.S. cancer surveillance system is that recurrence data are not collected routinely. Improved methods for monitoring the global burden of cancer also are needed, as existing data indicate increasing rates of breast cancer with global modernization and suggest that the global burden of breast cancer will grow substantially. Scientists will need to monitor the global changes in the burden of this disease and conduct studies to rapidly ascertain the causes.

3.9 Conclusion

Breast cancer has a large impact on the people who live with it, their families and communities, and the health care system. Breast cancer is not one disease but many. It has different incidence and mortality patterns by gender and race/ethnicity. The number of breast cancer survivors is increasing, and those survivors require lifelong medical surveillance and, in many cases, additional treatment for cancer and/or treatment-related side effects. Cancer registries and surveillance systems are crucial for monitoring trends in breast cancer, identifying disparities, uncovering possible contributors to breast cancer trends, and assessing the success of interventions to control and treat the disease.

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4
CHAPTER

Major Advances in Breast Cancer Prevention, Diagnosis, and Treatment

The Breast Cancer and Environmental Research Act of 2008[a] specifically charged the IBCERCC with identifying and describing major advances in breast cancer research. The Committee reviewed the literature, consulted with breast cancer researchers, and identified many major research advances in breast cancer that have added to our collective knowledge about the causes, prevention, detection, and treatment of the disease.

The following list delineates some key research advances from both human and animal studies by major class of advance. References cited refer either to (1) the first definitive clinical trial; (2) studies that established a new direction that was built on or confirmed by later work; or (3) current reviews that have a perspective on the evolution of the science, such as epidemiologic studies that advanced the field and generated findings confirmed by subsequent studies. Bolded text identifies scientific advances directly relevant to the role of environmental factors in breast cancer risk.

4.1 Breast Cancer Prevention

- **Studies found that the timing of carcinogen exposures in the life course influences breast cancer risk (e.g., atomic bomb survivors and diethylstilbestrol [DES] daughters).[1, 2]**

- **Modifiable environmental factors that influence breast cancer risk were reviewed and classified by extent of risk, including alcohol consumption,[3] combined estrogen and progestin hormone therapy (HT),[1] physical activity, body mass index (BMI), and weight gain during adult life (high BMI and excess weight gain during adulthood confer increased breast cancer risk in postmenopausal women).[4]**

- The U.S. Food and Drug Administration (FDA) approved tamoxifen to reduce the risk of developing breast cancer among women at high risk for the disease.[5]

[a] Breast Cancer and Environmental Research Act of 2008, Pub L. No. 110-354, 122 Stat. 3984 (October 8, 2008). Available from: http://www.gpo.gov/fdsys/pkg/PLAW-110publ354/pdf/PLAW-110publ354.pdf.

- The Study of Tamoxifen and Raloxifene (STAR) demonstrated that raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer in postmenopausal women.[6] Raloxifene also was found to carry a reduced risk of endometrial cancer relative to tamoxifen, providing a safer alternative for women with an intact uterus.[7]

4.2 Breast Cancer Diagnosis

- Screening mammography was developed, resulting in a reduction in relative risk of breast cancer mortality for women ages 40 to 69.[8] The value of mammography for reducing breast cancer mortality, however, continues to be evaluated.

- The American College of Radiology developed the BI-RADS lexicon to standardize the terminology for reporting and communicating mammography results.[9]

- Researchers found that women with dense breasts have an elevated breast cancer risk.[10]

- BRCA1 and BRCA2 gene mutations were linked to an increased risk of breast cancer—a finding that helps identify individuals at increased risk.[11,12] Currently, there are no standard criteria for recommending or referring someone for BRCA1 or BRCA2 mutation testing.[13]

- Magnetic resonance imaging (MRI) screening begins to be used to screen women with high breast cancer risk based on genetic factors.[14, 15]

- Gene expression profiling is used to define breast cancer as at least five subtypes, each with its own molecular signature.[16, 17]

4.3 Breast Cancer Treatment

Surgery

- Clinicians transition away from radical mastectomy to lumpectomy and radiotherapy, reducing the extent of surgery and adverse outcomes/morbidity for breast cancer patients.[18]

- Sentinel lymph node (SLN) biopsy was found to be a safe and less invasive means of assessing lymph node involvement in patients with breast cancer to determine prognosis.[19]

Adjuvant Therapy

- Adjuvant chemotherapy was developed and found effective in reducing the risk of breast cancer recurrence and mortality.[20]

- Improved radiation therapy using novel imaging techniques was developed to allow enhanced, targeted dosing to specific locations and reduced risk of irradiation of normal breast tissue and surrounding non-breast tissue (i.e., heart, major vessels, and lung).[21]

- Tamoxifen, an adjuvant hormonal therapy, was found effective, and clinicians began to use estrogen receptor (ER) status to guide decisions to use endocrine therapy.[22]

- Aromatase inhibitors were established as an appropriate treatment for ER+ tumors in postmenopausal women instead of tamoxifen, before or after tamoxifen treatment, or after 5 years of tamoxifen treatment.[23]

- Herceptin (trastuzumab), a monoclonal antibody and one of the first of a new generation of targeted therapies, was found effective in the treatment of breast cancer that expresses the HER2 protein.[24]

Treatment Decision-Making Tools

- A 21-gene recurrence score model was developed to assess the risk of breast cancer recurrence in women with node-negative, ER+ cancer and predict the magnitude of chemotherapy benefit (Oncotype Dx).[25]

- MammaPrint, a gene expression-based prognostic test to assess a patient's risk of developing metastasis, was developed.[26]

4.4 Animal Research

- Scientists developed a carcinogen (7,12-dimethylbenz-alpha-anthracene [DMBA])-induced model of mammary cancer in rats and mice and used it to evaluate individual susceptibility.[27, 28]

- Scientists conducted cell type-specific localization and functional analysis of ER and progesterone receptor (PR) isoforms in mammary tissue.[29-33]

- Rodents were used to test the efficacy of drugs for breast cancer treatment and prevention (e.g., tamoxifen, raloxifene, and aromatase inhibitors).[34, 35]

- **Studies provided data for the IARC report (1987) and Report on Carcinogens (RoC),[36] focusing on steroidal estrogens as carcinogens.[36, 37]**

- **Environmental agents and carcinogens (e.g., dioxin, bisphenol A [BPA], and diet) that affect the risk of mammary tumor development in animal models (primarily rats and mice) were identified.[38-40]**

- Underlying mechanisms that mediate the protective effect of pregnancy on cancer were analyzed.[41-44]

- An assay was developed to test the efficacy of drugs for breast cancer treatment and prevention (e.g., tamoxifen, raloxifene, and aromatase inhibitors).[45-47]

- Comparative anatomy studies (rat/mouse and rodent/human) clarified similarities and differences between species.[48, 49]

- Genetically modified mouse lines elucidated genetic and developmental bases for tumor susceptibility.[50-54]

- Growth factors were identified that are critical to mammary growth and development.[55-59]

- Studies enhanced understanding of the role of the microenvironment in tumor progression (e.g., stromal role, epithelial-stromal cell interactions, composition of extracellular matrix).[60]

- Mammary stem/progenitor cells were identified and their regulation and potential role in mammary carcinogenesis examined.[44, 61-64]

- **Studies demonstrated the modifying role of dietary fat, fat metabolism, and inflammation in tumor risk.[65-67]**

- **Scientists identified chemicals that modify mammary development by disrupting endocrine systems (atrazine, perfluorooctanoic acid, and dioxin).[68-73]**

- **Non-DNA mediated irradiation effects on mammary stroma were identified.[74, 75]**

- **The National Toxicology Program (NTP) added the assessment of mammary development and early life exposures as standard practice in its Reproductive and Continued Breeding bioassay and in the 2-year cancer bioassay.[36, 76, 77]**

- Scientists identified the basis for increased breast cancer risk during postpartum involution (the shrinking of milk-producing structures of the breast to their pre-pregnancy size following weaning).[78, 79]

Many of these advances might not have occurred if it were not for the powerful force of breast cancer advocates demanding research in these areas. Breast cancer remained a hidden disease among women in the United States until the 20th century, when it was brought into the open with public revelations from individual women who were supported by their family members, friends, community, activists, advocates, and policymakers.[80] For example, Rose Kushner publicly questioned the Halstead radical mastectomy (a procedure that removed the breast and pectoral muscles with debilitating results) as the standard breast cancer treatment. She became the catalyst for women to question standard medical practices at that point in time.[80] The early efforts of women like Mary Lasker, who made cancer research a priority,[80] and Rachel Carson, who raised awareness about cancer and environmental factors, also played a significant

The breast cancer activism movement did not happen in a vacuum; it was simultaneously influenced by AIDS-related activism[82] and the feminist and women's health movements, both of which encouraged women with breast cancer to (1) provide peer-to-peer information and support through organizations such as the American Cancer Society's (ACS) in-person Reach to Recovery program and the Y-ME National Breast Cancer Organization's telephone hotline; (2) take a more active role in treatment decisions; (3) lobby their legislators for more research and access to screening and treatment services; and (4) interact with researchers in novel ways.

Throughout the breast cancer activism movement, women have not acted alone. Groups of women have had a strong impact on the advancement of breast cancer prevention, detection, and treatment. Community grassroots organizations—such as Zero Breast Cancer on the West Coast, and the Huntington Breast Cancer Action Coalition and the One in Nine: The Long Island Breast Cancer Coalition on the East Coast; as well as national advocacy groups like the Breast Cancer Fund in California—emerged in the 1990s and advocated for breast cancer research funding.[83] The One in Nine: The Long Island Breast Cancer Coalition and the Silent Spring Institute specifically advocated for funding of research on the environmental links to breast cancer.[83] The National Breast Cancer Coalition played a pivotal role in framing breast cancer not only as a health issue but as a political issue that could be influenced by public policy and pressure.[84, 85]

As a result of these organizations' actions and voices, federal funding has expanded for research on breast cancer in general and on environmental influences on breast cancer specifically. For example, the National Institute of Environmental Health Sciences (NIEHS) and the National Cancer Institute (NCI) have jointly funded ongoing transdisciplinary research on breast cancer and the environment. Advocacy efforts also led to the creation of the Department of Defense (DoD) Breast Cancer Research Program (BCRP), a peer-reviewed program to fund breast cancer research in general, administered by the U.S. Army Medical Research and Materiel Command.[86] In addition, women who advocated for research on breast cancer and the environment have had meaningful interactions with research scientists across disciplines that has led to changes in the way that both biomedical and environmental scientists work.[87]

During the past decades, advocates and community stakeholders have played important roles in the prevention, diagnosis, and treatment of breast cancer by increasing awareness, developing research priorities, participating in the research process, and advocating for policy changes. Advocates have been particularly effective at increasing awareness of the need for research on the relationship between environmental exposures and breast cancer. Breast cancer advocates have adopted environmental causes as a concern, and environmental advocacy groups have adopted the mission of breast cancer. Both groups have lobbied for improved coordination of research across federal agencies; and scientists and advocates have worked together to plan, review, and conduct research and translate and disseminate its results. Section 4.5 provides a timeline of advocacy milestones in the advancement of research on breast cancer and the environment. Many of the organizations and initiatives mentioned in this timeline are described in greater detail in Chapter 7.

4.5 Milestones by Advocacy Groups in Advancing Breast Cancer Research and Research on Breast Cancer and the Environment

Early 1980s and early 1990s

Several large nonfederal organizations (NFOs) emerged or included as part of their mission a focus on supporting and fostering research and/or the involvement of advocates in breast cancer research decisions and studies. These NFOs included the

Susan G. Komen Breast Cancer Foundation (now Susan G. Komen for the Cure) in 1982, National Breast Cancer Coalition (NBCC) in 1991, and Avon Foundation (now Avon Foundation for Women) in 1992.[85]

Early 1990s

Across the United States, individuals established organizations to focus on the physical and chemical causes of high rates of breast cancer. Organizations with a focus on breast cancer causes included local grassroots organizations, such as the Marin County Breast Cancer Watch (now known as Zero Breast Cancer), Massachusetts Breast Cancer Coalition, Women's Cancer Resource Center in California, Women's Community Cancer Project in Massachusetts, Huntington Breast Cancer Action Coalition, West Islip Breast Cancer Coalition, and One in Nine. Others include national advocacy organizations such as Breast Cancer Action and the Breast Cancer Fund.[85]

1992

NBCC's advocacy efforts led Congress to authorize and appropriate an unprecedented $210 million for a breast cancer research program within the DoD.[88] As a result of advocates' continued efforts, the BCRP has received more than $2.6 billion in congressional appropriations through 2011, supporting more than 6,100 research grants.[88, 89] Consumer advocates are equal voting members in the peer and programmatic review of every DoD BCRP proposal.[86]

1993

Advocacy efforts in New York led Congress to mandate the $30 million Long Island Breast Cancer Study Project (LIBCSP) to investigate whether environmental factors were responsible for breast cancer in Suffolk and Nassau Counties (Long Island, NY) as well as in Schoharie County, NY, and Tolland County, CT. Along with the DoD BCRP, the LIBCSP was one of the first programs to involve advocates and breast cancer survivors in peer review committees.[90]

1993

Spearheaded by the Breast Cancer Fund and Breast Cancer Action, advocates' efforts led to the establishment by the California legislature of the California Breast Cancer Research Program (CBCRP). The CBCRP focuses on adopting research strategies and allocating funds to support studies in breast cancer biology, causes, prevention, treatment, and survivorship.[91]

1994

Activists led by the Massachusetts Breast Cancer Coalition (which questioned the elevated breast cancer rates throughout Cape Cod and called for an investigation into potential causes) founded the Silent Spring Institute to investigate potential physical and chemical causes of breast cancer.[92]

1995

NBCC created Project LEAD (Leadership, Education, and Advocacy Development) for teaching breast cancer advocates about science and the research process to enable them to bring an educated consumer perspective to breast cancer research and related activities.[93]

1997

In response to needs expressed by the cancer advocacy community, NCI formed the Office of Liaison Activities (now the Office of Advocacy Relations) to include people affected by cancer in NCI activities and programs.

1998

Many advocacy groups lobbied Congress to pass legislation to create the Breast Cancer Research Stamp.[94] The legislation mandated that 70 percent of funds raised from the stamp go to NCI, and 30 percent to the DoD BCRP. Since the Breast Cancer Research Stamp first went on sale in 1998 through October 2011, it has raised more than $73.5 million.[95] Currently, the stamp funds support work on racial disparities in breast cancer and triple-negative breast cancer.

2002

California advocates spearheaded the International Summit on Breast Cancer and Environment: Research Needs at the University of California, Berkeley, with funding from the Centers for Disease Control and Prevention (CDC), NIEHS, and the International Agency for Research on Cancer (IARC).[96]

2002

At the prompting of advocates, the NIEHS Director initiated dialogues with the public that led to the Public Interest Partners (PIP) (formerly the Public Interest Liaison Group) and grant programs focused on community-based prevention/intervention research and environmental justice.[97]

2003-2010

NIEHS and NCI initiated the Breast Cancer and Environment Research Centers (BCERC), a multidisciplinary, 7-year project to study the prenatal-to-adult environmental exposures that predispose a woman to breast cancer.[87, 98] This initiative was based in part on a 2002 brainstorming session with patient advocates, breast cancer specialists, and scientists. The Centers focused on determining the role of environmental factors in the onset of puberty in girls to better understand the development of breast cancer and ways to prevent it, and on animal model research to understand mechanisms of breast cancer development. The Avon Foundation provided additional support for BCERC projects. Based on the success of the first funding period, NIEHS and NCI decided to continue their support of research on breast cancer and the environment with a 5-year Breast Cancer and Environment Research Program (BCERP).

2008

As a result of advocates' efforts, Congress passed the Breast Cancer and Environmental Research Act that mandated the formation of a committee on breast cancer and the environment that produced this report. This Committee includes a number of advocates.

2009

Representatives of community and national organizations advocating for environmental justice and public health participated in six working groups convened as part of the *National Conversation on Public Health and Chemical Exposures*. Through these working groups, public forums, and significant public engagement and involvement, recommendations were developed for steps government agencies and other organizations can take to protect the public from harmful chemical exposures.[99]

2010

Advocates provided written and verbal testimony at the President's Cancer Panel's town hall meetings that formed the basis of the Annual Report of 2008 to 2009. This landmark review of environmental exposures concluded that "the true burden of environmentally induced cancer has been greatly underestimated."[100]

2010

Advocates presented and provided input to the Institute of Medicine (IOM) committee that reviewed and assessed the strength of scientific evidence on the relationship between breast cancer and environmental risk factors. Report findings were released in 2011 and called for a life-course approach to future breast cancer and environment research.[101]

In summary, important scientific advances have led to an improved understanding of how breast cancer develops and how to prevent, diagnose, and treat this disease. At the same time, the breast cancer advocacy movement has been critical in keeping attention focused on breast cancer and ensuring that substantial research funding is directed toward this complex disease and that advocates and community members are integrated into the research enterprise.

4

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5

CHAPTER 5

State of the Science: Part 1—Principles, Approach, and Mechanisms

5.1 Introduction

The Congressional legislation that established the IBCERCC specified that the Committee's report review the research findings and outline key research questions, methodologies, and knowledge gaps to evaluate environmental and genomic factors that may be related to the etiology of breast cancer. This chapter lays the foundation for a review of the state of the science by describing the transdisciplinary approach to research that applies the animal-to-human research paradigm mentioned in Chapter 2. This chapter also reviews normal mammary gland/breast development and its regulation across the life span, as well as mechanisms of cancer development, to provide context for the research reviewed in Chapter 6. State of the Science: Part 2.

5.2 Principles for Reviewing the State of the Science

5.2.1 Windows of Susceptibility and Timing of Exposure

The mammary gland undergoes many stages of development (i.e., *in utero*, neonatal, pubertal, sexual maturity, pregnancy, lactation and lactational involution, post-involution) across the life span. These stages are regulated by endogenous physiology (i.e., hormones, growth factors, inflammatory processes, epithelial-stromal interactions, and metabolism originating from within the body). Epidemiologic and experimental animal studies demonstrate differences in mammary cancer risk and sensitivity to potential cancer-producing or cancer-promoting factors at different developmental stages—referred to as "windows of susceptibility." This report considers the evidence for the cumulative effect of a wide range of exposures during many windows of susceptibility across the life course. The cumulative effects of exposures during windows of susceptibility can be examined in human as well as animal studies because rodents and other mammals experience the stages of mammary gland development similar to those experienced by humans, albeit during a shorter time frame.

Timing matters: The breast is especially sensitive to environmental exposures during fetal development (when the organ is formed), and during puberty and pregnancy.

Timing of exposure refers to the period/age when an individual is exposed to certain factor(s) during his or her lifetime. Observational studies of human

populations can record the timing of exposures and measure certain agents in tissue samples taken from the human body (e.g., blood, serum, urine) at different points in time. Studies that attempt to determine the amount of a person's exposure to certain agents at specific points in time across the life course, however, are difficult to conduct and complicated by a variety of factors (e.g., participants dropping out of studies, differences in the way individuals metabolize different chemicals). Experimental animal studies, on the other hand, allow scientists to control the timing and amount of an exposure. Both human and animal studies suggest a link between the timing of an environmental exposure (usually early in life, based on research to date) and the clinical appearance of breast cancer later in life. Scientists do not know, however, when a woman who develops breast cancer was exposed to a carcinogen (i.e., a chemical or physical agent capable of causing cancer), or the period of time between this exposure and the development of breast cancer (known as the latency period).

5.2.2 Animal-to-Human Research Paradigm

Research that is reviewed in this report falls into two major categories: (1) human observational epidemiologic studies (prospective and retrospective) and some human clinical trials; and (2) experimental exposure studies using living animals (*in vivo*) or cell cultures in a test tube *(in vitro*). The integration of animal and human research offers the best opportunity to understand the contribution of environmental factors to breast cancer risk, the underlying mechanisms, and the potential for prevention strategies. Studies of animal models can be used to generate hypotheses for human studies as well as aid in the interpretation of the findings from human research. On the other hand, human studies generate questions that can be tested under controlled conditions with animal models. Animal models have the added benefit of allowing researchers to examine the life span over a shorter period of time. In addition, because it is unethical to expose humans to certain chemicals and doses, certain compelling questions only can be studied using animal models and cell cultures. Integration of findings from both types of studies accelerates scientific knowledge and may improve the understanding of the applicability of animal models to human research. This and the following chapter employ an "animal-to-human" paradigm that attempts to integrate findings from animal and human studies to inform specific aspects of knowledge about the environmental causes of breast cancer. The Committee appreciates the need to evaluate the relevance of animal studies to humans with the understanding that differences in metabolism, uptake, excretion, half-life, dose, genetic background, and breast cancer subtype may appear in animals compared to humans.

The integration of animal and human research offers the best opportunity to understand the contribution of environmental factors to breast cancer risk, the underlying mechanisms, and the potential for prevention strategies.

Studies in human populations are critical to identify potential risk factors (e.g., diet, reproductive history, light at night exposures) as well as test findings from animal studies for their utility in the prevention and treatment of breast cancer in humans. Naturally occurring environmental disasters have led to research on populations exposed to high levels of specific environmental factors (e.g., radiation in atomic bomb victims; dioxin exposures in Seveso, Italy; chemical workers in Germany.[1, 2] These studies have led to the identification of differences in susceptibility to environmental contamination at different ages.[3-8] Human research also has the potential to examine the combined effects of characteristics of study participants that may be related to both exposure and breast cancer risk (e.g., socioeconomic status, health care access, genetic polymorphisms). Unraveling the effects of multiple factors, however, can be difficult. Strong evidence of an association between an environmental exposure and breast cancer risk can be obtained through well-designed studies that have appropriate sample sizes, address potential sources of bias, and use statistical analyses that examine multiple factors simultaneously. A single human observational study or several studies

sometimes yield sufficient evidence for causality. Data from multiple sources, such as human and animal studies or studies of underlying biologic mechanisms, usually are needed to determine whether a risk factor causes a disease. Criteria have been developed for establishing causality in epidemiologic studies. The Bradford Hill criteria, for example, include strength of the association, whether there is a dose-response relationship between the exposure and the disease, and whether the association is biologically plausible in determining causality.[9]

Animal studies provide the context and opportunity to design experiments with strict controls on factors that cannot be controlled in human research. For example, an experiment can be conducted in one genetically modified rodent strain or across different strains that mimic the heterogeneity in human populations.[10, 11] Such studies can focus on a specific developmental stage (e.g., puberty, pregnancy) to test the relationship of one or multiple environmental factors on breast cancer. Moreover, animal studies can determine whether an environmental factor is a carcinogen and whether or not it is capable of initiating changes in the cells or acts to promote/potentiate breast cancer through different mechanisms that stimulate the growth/spread of susceptible or altered cells.[12] Another important contribution of animal and cell culture studies is the ability to test the effects on the mammary gland or mammary-specific cell types of environmental factors (e.g., chemicals, hormones, lifestyle factors) that are suspected to have health effects but have not been identified by previous epidemiologic studies.[13]

Bisphenol A (BPA) research provides an example of how animal studies can reveal the effects of environmental chemicals on the mammary gland. BPA was found to have estrogenic activity in early laboratory studies of rats.[14] Since Dodds' and Lawson's pioneering study, dozens of studies have supported the estrogen-like activities of BPA on the mammary gland, other endocrine-responsive tissues, and the brain.[15, 16] Rodent studies repeatedly have shown BPA's ability to disrupt mammary gland development and, at sufficiently high exposure levels, lead to preneoplastic and neoplastic lesions with and without a second insult.[17-22] Further discussion of BPA can be found in Chapter 6 and Appendix 2. Although Chapter 6 describes a number of chemicals that have been linked to breast cancer, BPA is used as an example throughout this report to illustrate issues related to research on endocrine-disrupting compounds and chemicals that may impact breast cancer risk in general.

Experimental animal studies also can be used to develop and test methods to prevent breast cancer. For example, genetically modified mouse models have been used to identify the mechanisms by which chemopreventive agents may delay tumor development, suppress tumor multiplicity, and cause tumor regression in individuals with specific mammary cancer subtypes and risk factors, such as obesity.[23] Research using mouse models also identified the potential for aromatase inhibitors to reduce mammary tumor growth as well as mechanisms for delaying the development of resistance to aromatase inhibitors.[24] Findings from these studies were later tested in and applied to human populations.

High-quality, published research studies that use cellular systems, animal models, clinical approaches, and epidemiologic methods to study breast cancer all are important for understanding breast cancer etiology. Findings from each of these approaches can inform, build upon, and inspire research using the other approaches. In many cases, work done in a single laboratory or research group makes a substantial contribution to the greater body of scientific literature. In some unique situations, investigators from multiple disciplines collaborate to produce studies that work across the animal-to-human research paradigm. These collaborations can result in the (1) identification of new transdisciplinary hypotheses to test in either animal models or human populations; or (2) awareness of the need to replicate research results under different conditions. Using the animal-to-human research paradigm offers an excellent opportunity to accelerate progress in understanding breast cancer and the environment and translate research findings into clinical practice.

5

5.3 The Approach for Reviewing the Evidence

In reviewing the evidence, the Committee evaluated observational research and clinical trials in humans that examine different environmental and personal factors that might be related to breast cancer risk and/or survival, as well as findings from laboratory studies of animals. Although randomized clinical trials may have been considered the "gold standard" in the past, the Committee supports a more contemporary approach wherein the randomized clinical trial no longer is seen as the superior study design in all situations.[25] Green posited that dissemination of findings from human controlled clinical trials to the public requires more attention to the external validity and cautioned that "variability in settings, populations, cultures, and historical circumstances for public health makes the generalizability of overly controlled experimental research findings dubious to practitioners and policy makers."[25]

The Committee's review of the state of the science began with identifying recent review articles. For example, we selected the review articles by Brody and colleagues,[26] Rudel and colleagues,[13] and the State of the Evidence monograph by the Breast Cancer Fund[27] as starting points for reviews related to physical and chemical agents and breast cancer. The Committee found many additional recent publications (up through December 2011) using PubMed and Google searches. Search terms in PubMed and Google included the breast cancer risk factors identified in the review articles and other terms relevant to each risk factor. Although the formal evidence review included information published through the end of 2011, evidence published in 2012 was added when the Committee determined that the more recent evidence added strong value to the review. Both published and in-press articles were considered for inclusion. Because of the breadth of literature, the review in this report is not all-inclusive but highlights the most important publications.

5.4 Breast Cancer Etiology

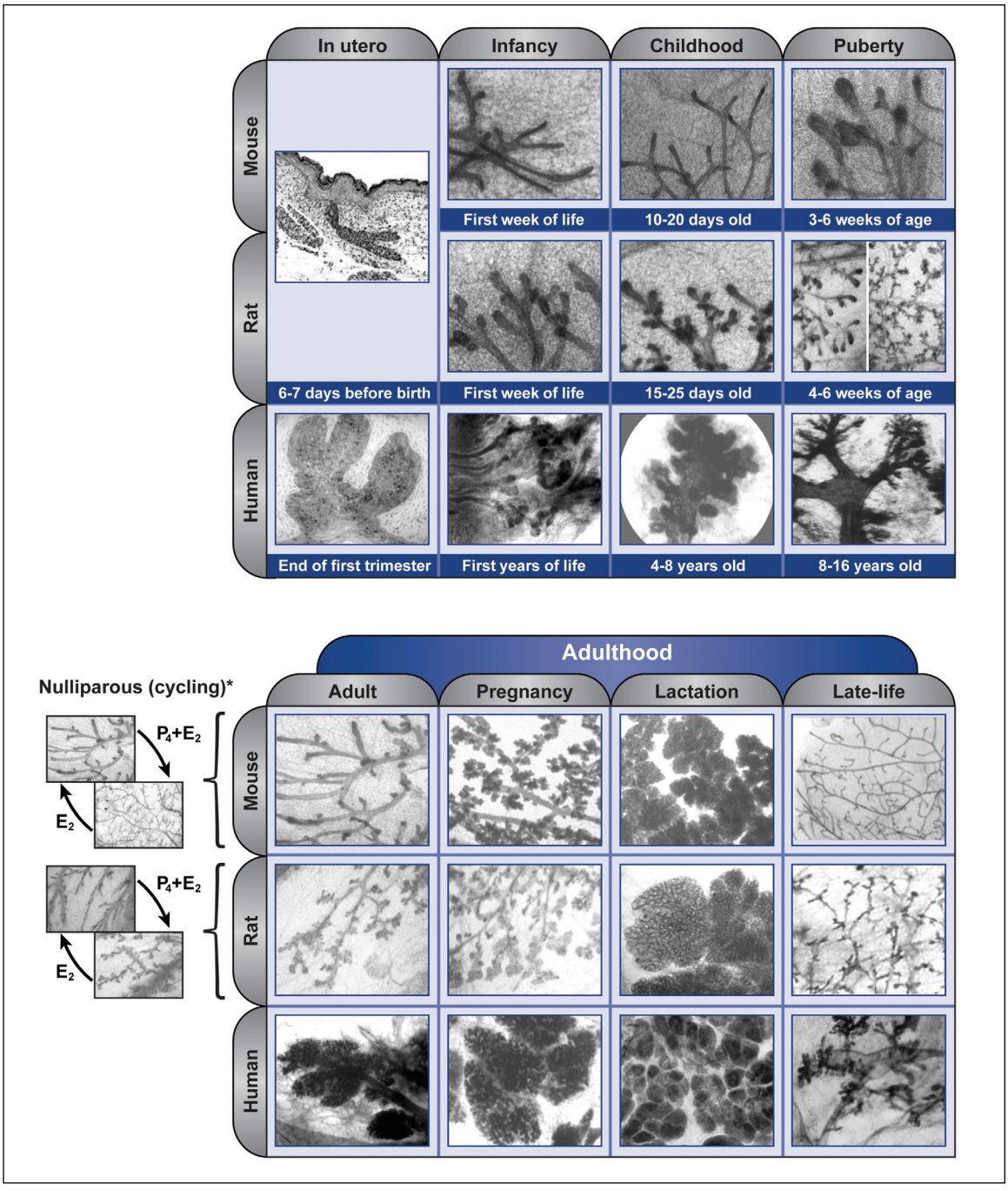
5.4.1 Normal Breast Development and Regulation Throughout the Life Course

To understand the role of the environment in the etiology of breast cancer, we first must understand breast and mammary gland development over the life course, including the life stages when this organ is most susceptible to environmental insults. Figure 5.1 illustrates the development of the mammary

To understand the role of the environment in the etiology of breast cancer, we must understand life stages when the breast is most susceptible to environmental insults.

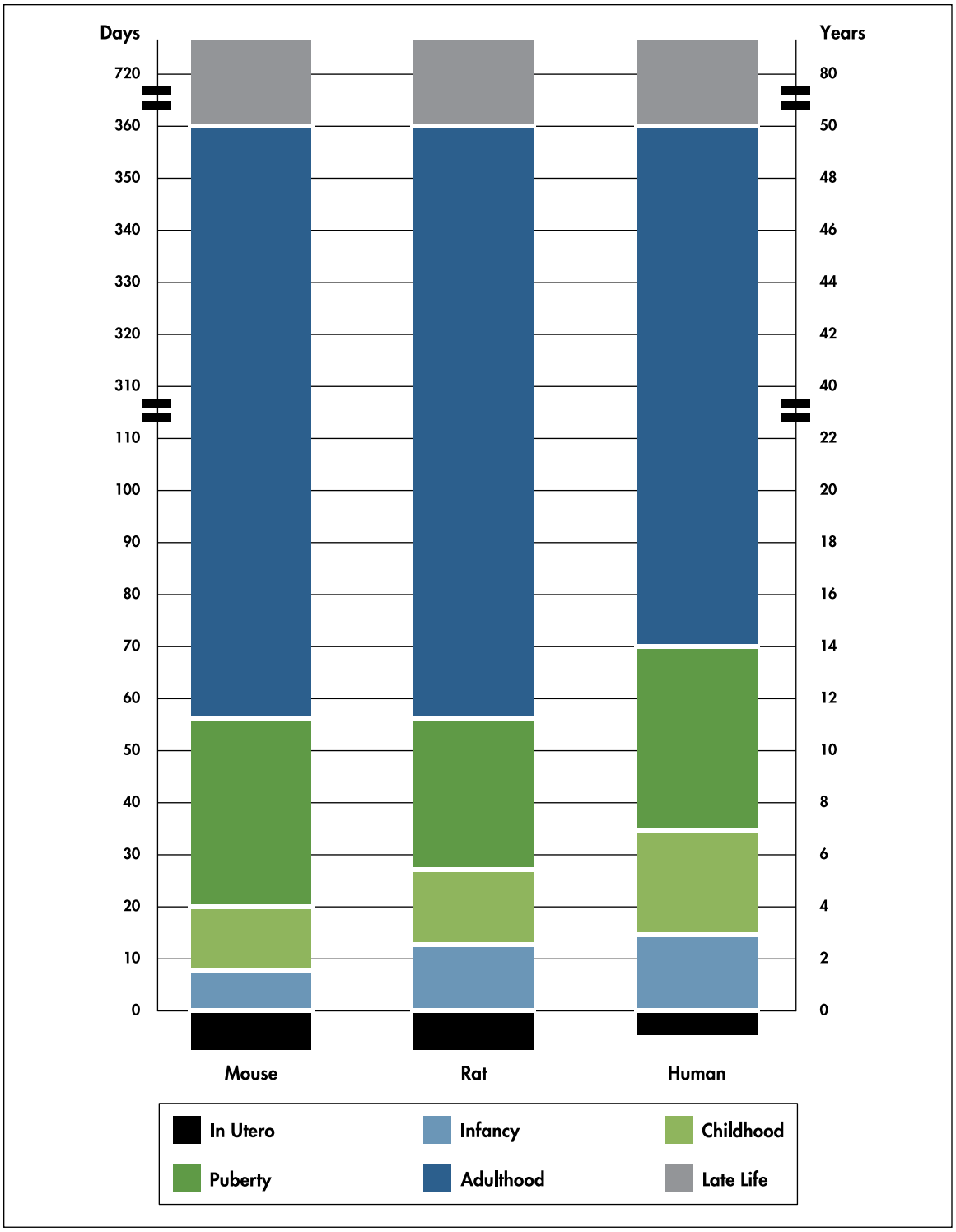
gland at different life stages for the human, rat, and mouse. Figure 5.2 compares the relative duration of time each species spends in each stage of mammary development. The mammary gland is one of the few organs that primarily develops after birth and is part of pubertal progression and lactation in all mammals. A rudimentary system of ducts is formed by birth. The scant data available suggest that human embryonic development of the breast begins with budding and branching late in the first trimester of pregnancy and results in the rudimentary gland present at birth.[28-30] For the rodent, initial development begins during late pregnancy (6–7 days before birth).[31] After birth, rodent and human mammary glands grow at the same rate as the body. Just before puberty, the mammary gland begins growing at a faster rate than the body. During the period of rapid growth that occurs in puberty, the epithelium (the mammary cells that may eventually produce and secrete milk) rapidly fills the mammary fat pad with a network of branched ducts with terminal end buds (TEBs). The TEBs proliferate and differentiate into structures referred to as terminal ductal lobular units (TDLUs) in humans, which are similar to alveolar buds in rats and more primitive terminal ducts in mice. The TDLU structure in humans

Figure 5.1. Structure of the mammary gland during the different life stages of the mouse, rat, and human



In this comparison of the rodent mammary gland and human breast over the life course, mouse and rat tissues are magnified 1.8 times and human tissue is magnified 2.5 times (rat tissues at 4–6 weeks are less magnified than mouse and human tissues at the same age). Evaluation of similar life stages demonstrates the similarities and differences between the rat and mouse mammary glands and the human breast. In childhood, puberty, and adulthood, the mouse demonstrates a more simple ductal morphology (lacks buds and lobule development) than the rat and human. During adult life, all species demonstrate morphological changes in lobule development characteristics reflective of differences in cycle-dependent ovarian hormone levels (E_2, estradiol; P_4, progesterone). This figure does not show the cyclic changes in the human breast. Numerous morphological similarities are evident across species during pregnancy and lactation. Regression of the mammary ducts and lobules to a static state is seen late in life in all species. Source: Fetal mammary gland micrographs for rat and mouse from Cowin and Wysolmerski;[35] micrographs for all other stages from S.E. Fenton and S.Z. Haslam [unpublished]. Human breast micrographs were contributed by J. Russo.[36] Male tissues are not shown for rats and humans due to the lack of representative data in the literature.

Figure 5.2. Comparison of the relative time spent in the different stages of mammary gland development for mice, rats, and humans



Mammary development begins 6-7 days before birth in the rodent or about 6 months before birth in the human and follows the same course, with similar relative time spent in each life stage. Breaks in time in Figure 5.2 are denoted by hash marks.

is surrounded by fat cells without intervening fibroblastic stroma (the connective, functionally supportive framework of the breast tissue).[29, 30] The TDLUs are the major hormone-sensitive areas of the mammary epithelium and the functional precursors of the mammary gland. TDLUs also are the site of origin for most mammary cancers.[30, 32]

Figure 5.2 shows how the developmental stages of the mammary gland in rodents and humans occur at a similar biologic pace, supporting the use of mice and rats as models for human breast cancer studies.[33] The figure also reflects the dramatically shorter life span of rodents relative to humans. The human postmenopausal stage is not seen in rodents. During this stage, the lobules and ducts decrease in size and number, the stroma contains increased levels of collagen, and the area previously occupied by glandular epithelium is replaced by fat cells.[29]

Current evidence suggests that, similar to humans, rodent mammary epithelial cells are maintained by the unique properties of stem cells. Stem cells have the capacity to generate all of the epithelial cell lineages (basal, myoepithelial, luminal, alveolar) and allow the mammary gland to undergo proliferative expansion during puberty and pregnancy as well as regeneration after changes during menstrual/estrous cycles and lactational involution.[34]

Ovarian steroids estrogen and progesterone play a major role in the different stages of mammary gland development. Their activity and function can be affected by other factors that regulate ovarian steroid production, such as activity of the aromatase enzyme in fat tissue and pituitary hormones, including luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin.[37, 38] Estradiol, an estrogen, is critical for ductal epithelial cell proliferation after birth. At puberty, estradiol is the major driver of ductal development. Ovarian steroids also cause changes in the mammary gland after sexual maturity (proliferation and regression) that depend on the stage of the menstrual (human) or estrous (rodent) cycle. In particular, progesterone plays a key role in the proliferation of the mammary gland during estrous/menstrual cycles. Estrogen and progesterone act together to promote proliferation and differentiation (the process by which a cell develops into a more specialized or less proliferative state) of breast epithelial cells during pregnancy.[39] Postpregnancy, the differentiated gland produces and secretes milk under the control of cortisol and prolactin. Mammary gland involution occurs after lactation during weaning and involves regression and removal of the epithelium by phagocytosis (the process by which one cell engulfs another cell).[29, 30, 40, 41] The estrogen receptor (ER) (which binds estrogen) has two nuclear subtypes, alpha and beta (ERα and ERβ). In humans, ERα is present in mammary epithelium from 30 weeks of gestation onward,[42] and a similar pattern is seen in the rat.[43] ERα is predominant in the adult breast (ERβ is expressed only in a small proportion of the epithelium).[44] Studies in mice have demonstrated that ERα in the epithelium is largely responsible for estrogen-induced growth of the mammary gland.[44, 45]

Studies indicate that progesterone indirectly controls the number and activity of normal breast stem cells (immature cells from which other cells derive).[46,47] In rodents and humans, the downstream actions of progesterone in the development of the normal mammary gland and breast cancer are thought to be similar.[48-50] The progesterone receptor (PR) produces two different forms, or isoforms, of protein. These isoforms, PRA and PRB, appear in equal quantities in the normal human and rat mammary gland. In humans, expression of both PRA and PRB is regulated by estrogen (expression is the process by which information from a gene is used to create a functional gene product, usually a protein). In rats and mice, PRB expression is less dependent on estrogen and its regulation is less well known. In mammary cancer, more PRA is found relative to PRB.[50] Scientists have hypothesized that this imbalance, caused by a loss of coordinated expression of PRA and PRB, is an early event in the development of breast cancer in the human and rat.[51, 52]

In addition to the ovarian steroids, many systemic and locally produced growth factors are involved in mammary gland differentiation in the embryo and

during growth and involution. These factors include growth hormone (GH), epidermal growth factor (EGF), hepatocyte growth factor (HGF), and insulin-like growth factor-1 (IGF-1). The contributions of these growth factors to mammary development, function, and tumor formation have been demonstrated in genetically modified mice.[53-57] Many pituitary hormones (e.g., FSH, LH, prolactin, GH) also affect mammary development and breast cancer risk. For example, prolactin consistently has been linked to increased mammary tumor formation in animal studies.[58] Extrapolation of findings from studies of hormones in animals to humans is difficult because of species-specific differences in the timing of postnatal maturation of the pituitary gland and the decline of pituitary gland function during aging.[37]

Like women, men possess hormonally responsive ductal epithelium at birth, but further growth is inhibited by pubertal and adult testosterone levels. Hormonal abnormalities, however, such as increased prolactin levels, can lead to gynecomastia (male breast development) and may lead to male breast cancer.[59-62] Rats likely are the best animal model for studying male breast cancer because male rats exhibit ductal outgrowth similar to growth in female rats.[13]

5.4.2 Developmental Periods Potentially Related to Breast Cancer Risk

The extensive proliferation of the mammary gland during puberty and the rapid expansion of the epithelium during pregnancy can create conditions that make the gland vulnerable to environmental factors that can increase cancer risk.[13, 33, 37, 63] Breast tissue remodeling after lactation ends also can create an environment in which the mammary gland is sensitive to exposures that may lead to cancer.[64-66] Studies of rodents have shown that the following periods in mammary development are the most sensitive to environmental influences: (1) *in utero* development; (2) neonatal development; (3) puberty; and (4) pregnancy.[33] During gestation, when the fetal mammary bud is developing, environmental factors can cause changes that lead to altered pubertal development and persistent physical abnormalities that result in impaired functioning of the gland in the adult rodent. Animal studies also have identified several examples of environmental exposures during neonatal and pubertal periods that extend the length of time that TEBs are present, potentially increasing the time period when the breast is sensitive to carcinogens.[33]

Few human studies have investigated how lifetime exposure to an environmental factor interacts with windows of susceptibility to affect the risk of breast cancer. The majority of these studies have focused on the effects of environmental factors in adulthood, around the time of disease diagnosis, and have not investigated changes in gland development and pathologies that might be caused by environmental factors during the earlier, potentially more sensitive periods of breast development identified in animal studies.[33] Some epidemiologic studies, however, have examined breast cancer risk in relation to factors that occurred at specific developmental periods (e.g., birth, infancy, pregnancy). For example, lower birth weight, twinning, maternal and personal pre-eclampsia, and having been breast fed all have been linked to decreased breast cancer risk.[67] Other studies have examined breast cancer risk related to increases in height during childhood[68] and childhood weight gain and growth.[69] Studies of high-dose radiation exposure during puberty/adolescence have suggested the importance of environmental exposures during breast development on increased breast cancer risk later in life, as have the recent findings by Cohn and colleagues on the role of the timing of DDT exposures during the life course.[70] The Breast Cancer and the Environment Research Program (BCERP), funded by the National Cancer Institute (NCI) and the National Institute of Environmental Health Sciences (NIEHS), will provide more

The majority of the studies on breast cancer and the environment have looked for environmental exposures at or around the time of diagnosis, although the causative exposures could have occurred decades earlier.

information on the effects of environmental exposures at puberty, but understanding the relationship between these exposures and breast cancer risk will require further research.

5.4.3 Mechanisms and Pathways of Cancer Development

The etiology of breast cancer and the molecular mechanisms that underlie the development and progression of the disease are not well understood. An understanding of the mechanisms of breast cancer development is complicated by the heterogeneous nature of the disease, with at least five different subtypes that may have different etiologies.[71]

Cancer develops when normal, tightly regulated cell proliferation is altered, resulting in uncontrolled growth and evolution to malignancy. This process can occur through the overproduction of growth stimulating factors, the reduced production or loss of cell proliferation inhibitors, defective DNA repair mechanisms, or the loss of balance between cell proliferation and cell death (apoptosis). These changes are caused by alterations in the genes that control these processes and can occur through mutagenic, epigenetic DNA-mediated, and non-DNA-mediated pathways. Cancers begin with an initiation event in which normal cells are changed so that they are able to form tumors. Initiation events are followed by promotion and progression phases.[72] Promotion is the process by which initiated cells proliferate to form precancerous hyperplasia (abnormal, uncontrolled epithelial growth). Progression occurs when the hyperplasia expands, evolves into cancer, and acquires the potential to metastasize (spread from one part of the body to another) and invade other organs. Metastasis to vital organs and loss of organ functions generally lead to death. Environmental factors may affect cancer outcomes throughout this entire cascade of events. Most of the known mechanisms involved in the development of breast cancer are illustrated in Figure 5.3.

DNA-Mediated Mechanisms

Mutagenic Mechanisms

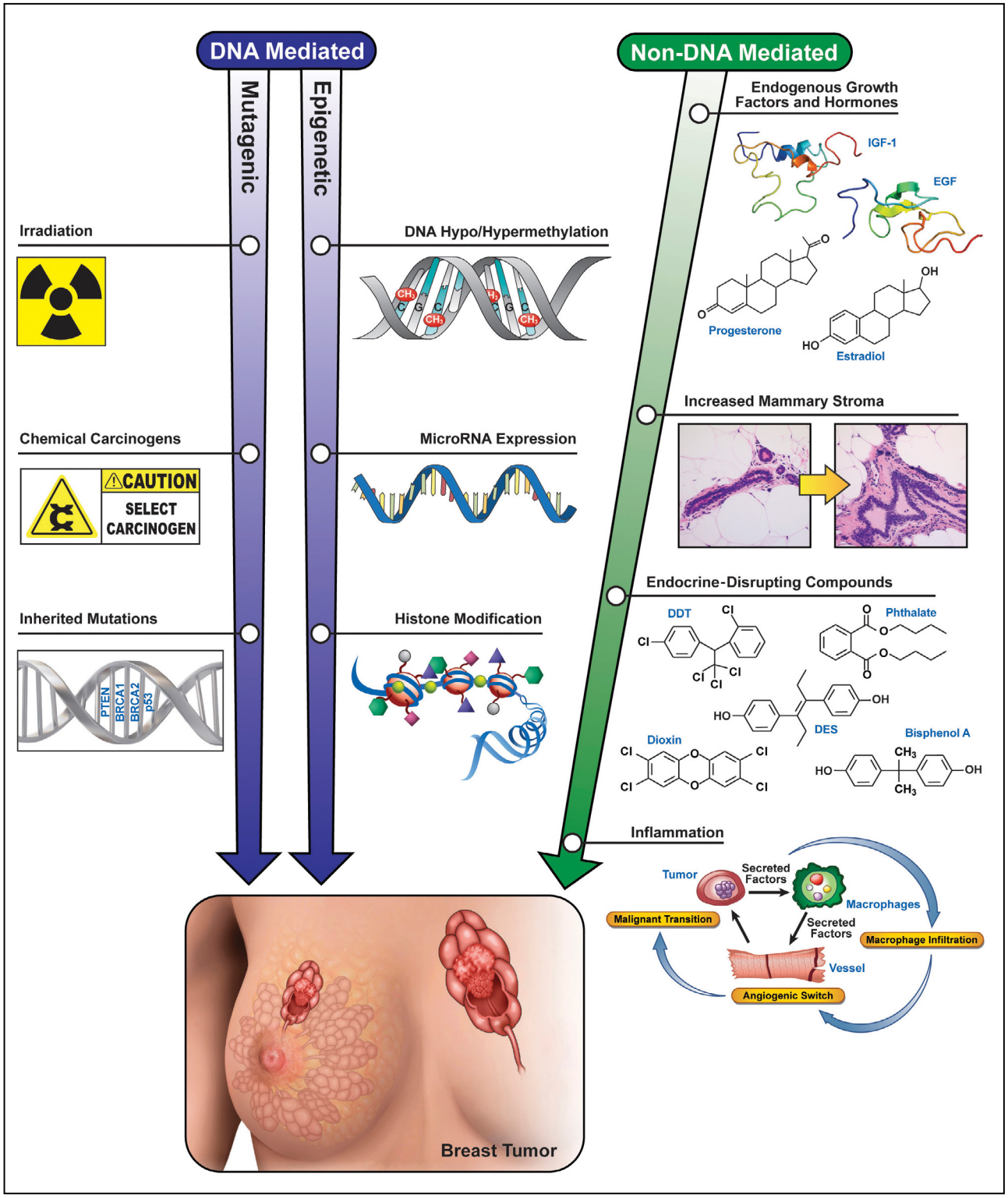
A mutagen is a physical or chemical agent that changes genetic material, resulting in an elevated frequency of mutation that increases the likelihood that cancer will occur.[73] Some of the most well-studied gene mutations are inherited. Inherited gene mutations, such as mutations to BRCA1 or BRCA2 (breast cancer susceptibility genes 1 and 2, respectively), may be enough to cause an elevated breast cancer risk. These types of mutations, however, account for a small fraction of all cancers.[74] In addition, sporadic breast cancer (cancer in people without a family history or an inherited change in DNA that increases their risk) often clusters in families without following direct inheritance patterns of a single-gene mutation, such that females with a sister or mother with breast cancer are more likely to develop the disease.[74]

Epigenetic Mechanisms

Breast cancer may arise through epigenetic mechanisms, which involve changes in gene expression that are caused by mechanisms other than changes in the underlying DNA sequence.[75] Epigenetic changes can be inherited and lead to phenotypic changes in the offspring.

One epigenetic mechanism that is associated with breast cancer involves changes in DNA methylation. For example, hypermethylation (an increase in the number of methyl groups added to the DNA in many places along the chromosome) has been shown to inactivate the tumor suppressor genes BRCA1 and TMS1.[76] A tumor suppressor gene encodes a protein that helps to control cell growth. Global DNA hypomethylation (a decrease in the methylation process) also has been linked to cancer and occurs in up to 50 percent of breast cancers in women.[77,78] Esteller[76] has studied multiple key cancer genes undergoing epigenetic inactivation in primary human tumors with

Figure 5.3. Mechanisms involved in breast cancer etiology



Numerous mechanisms are reported to be associated with increased breast cancer risk. These mechanisms fall into two main categories: DNA mediated and non-DNA mediated. Mutagenic factors affect the DNA sequence, whereas epigenetic factors modify the DNA conformation; both lead to heritable changes in breast cancer risk. Non-DNA mediated factors act in a more indirect manner, causing altered inflammatory response, changes in stromal tissue, or modified hormone actions. More than one mechanism may be involved in an individual's cancer risk.

the goal of identifying a subset of genes whose methylation was linked with malignant transformation. Breast and ovarian cancers tend to be associated with methylation of certain genes, such as BRCA1, GSTP1, and p16INK4a. Studies in rodents have shown that methylation changes can be reversed through interventions, such as dietary supplementation with B vitamins during gestation.[79]

Another epigenetic mechanism for inducing breast cancer involves histone modification (a modification to the several proteins that, together with DNA, comprise most of the chromatin in a cell nucleus). DNA methylation and histone modifications interact with each other in the regulation of gene expression.[80] Scientists have hypothesized that the epigenetic silencing of tumor suppressor genes through histone deacetylation and DNA methylation is an early sign of malignancy.[81, 82] Studies have found some evidence of different patterns of histone acetylation in normal breast epithelium, ductal carcinoma *in situ* (DCIS), and invasive epithelial lesions.

Scientists recently have become interested in the potential role of small, noncoding RNAs, or microRNAs (miRNAs), in the development of cancer. The miRNAs are RNAs that regulate messenger RNA (mRNA) translation (the stage of the gene expression process that produces proteins). The number of genes known to be regulated by miRNAs is growing rapidly.[80] The function of the target mRNA determines whether a miRNA will act in a manner that suppresses or promotes tumors.[83] Recent genome-wide analyses revealed that miRNAs are globally downregulated in breast cancer.[84] Scientists also are identifying deregulated miRNAs to determine mammary cancer subtypes or tumor aggressiveness.[80] Studies have shown that depletion of certain families of miRNAs in breast, lung, and colon cancer are associated with specific molecular/morphologic features[80] and that overexpression of miR-21 in breast cancer cells promotes metastasis to the lung.[85] Aberrant DNA methylation may explain, in part, how miRNAs can be upregulated (through DNA hypomethylation) or downregulated (through DNA hypermethylation) in cancer.[80]

Non-DNA-Mediated Mechanisms

Many of non-DNA-mediated mechanisms are thought to have a promotional rather than an initiating effect on breast cancer development. These promotional factors act on cells that have undergone permanent changes that make them susceptible to cancerous growth.[86]

Endogenous Growth Factors and Hormones

Endogenous hormones and growth factors can affect tumor development. Their growth-promoting effects are highly regulated in normal cells but can be subverted to promote uncontrolled growth in cancer cells. For example, transforming growth factor beta (TGFβ) acts as a tumor suppressor by inhibiting cell proliferation and inducing cell death in normal tissue, but can become a tumor promoter by inducing changes to mammary epithelial cells or undifferentiated cells in the developing embryo.[87-89] IGF-1, a growth factor that stimulates cell division and inhibits cell death, also has been associated positively with breast cancer risk in women.[90] EGF receptor ligands (molecules that bind to a receptor on the surface of a cell, including EGF, amphiregulin, and TGFα) also play important roles in both normal and cancerous breast growth. They bind to and activate the human epidermal growth factor receptor 2 (HER2/neu), which has been associated with the development and progression of certain aggressive types of breast cancer.[91]

Altered activity of endogenous hormones also can dysregulate normal mammary gland maturation and affect breast cancer risk. For example, leptin, a fat cell-derived hormone known for its role in energy balance, affects mammary gland development and function. Leptin-deficient mice are unable to support pups after birth because of undeveloped mammary glands. This hormone also may promote mammary tumor development. Studies of transgenic mice overexpressing leptin and fed a high-fat diet (which causes high serum levels of leptin) developed mammary tumors earlier than mice with lower leptin levels. Obese Zucker rats, which normally

have elevated leptin levels, showed an increased susceptibility to the effects of certain carcinogens on the mammary gland. When treated with the carcinogen 7,12-dimethylbenz(*a*) anthracene (DMBA), the obese Zucker rats had a mammary tumor incidence double that of the lean control group, a shorter tumor latency period, and a more invasive histopathology.[92] Studies of cell lines lend further support to the observed relationship between leptin and mammary tumors. For example, leptin has a demonstrated ability to interfere with the effects of the anti-estrogen ICI 182,780 in breast cells, suggesting that leptin status may alter the response to preventive treatments in some women.[93] Research on the association between leptin and breast cancer risk in humans, however, has demonstrated inconsistent results.[94]

Exogenous Factors—Endocrine Disruption

Exogenous chemical or lifestyle factors also may influence hormones and growth factors. An exogenous chemical that influences hormones or growth factors is known as an endocrine-disrupting compound (EDC), which the World Health Organization (WHO) defines as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations."[95] These chemicals are used in making plastics and pesticides and are present in consumer products such as furniture, metal food cans, and cosmetics.[96] National survey data show that many of these chemicals are present in the blood or urine of children and adults in the United States,[97] and some EDCs are present in 100 percent of the people sampled.[98] EDCs that mimic hormones or disrupt the function of endocrine system homeostasis (balance) are not necessarily carcinogenic themselves, but they may promote the formation and growth of cancer cells through a variety of mechanisms. These mechanisms include induction of receptors for carcinogens, creation of a stromal microenvironment suitable for hyperplastic growth, or initiation of uncontrolled DNA synthesis following mutations caused by carcinogen exposure.[99] Scientists believe that many EDCs work indirectly by mimicking or disrupting hormone-regulated pathways during important stages in mammary gland development.[13,27] Some EDCs may accumulate and be stored for long periods in fat tissue, so the amount of fat tissue surrounding TDLUs may be important to understanding breast cancer risk.[100, 101]

EDCs may change normal physiologic responses and give rise to metabolic and hormonal disorders later in life.[102] EDCs that interact with and change nonmammary organs, such as the ovary, pituitary or adrenal glands, or the immune system, also may impact mammary development through altered signaling between the mammary gland and these other organs or systems. For example, several EDCs are known to cause weight gain,[103] which is a known modifier of cancer risk and pubertal timing.[104] The effects of EDCs, therefore, could be multilayered because they act as direct (acting at the primary tissue site) and indirect (acting through another tissue to have effect) risk modifiers. In addition, EDC exposures can cause epigenetic changes that are thought to increase breast cancer risk and can be passed on to the next generation,[105] perpetuating the elevated breast cancer risk.

Mammary Stroma

Evidence increasingly supports the role of mammary stroma in tumorigenesis in both humans and rodents. The composition of and signaling from the mammary stromal extracellular matrix can alter the hormone responsiveness of human tumor cells,[106] and normal mammary development.[107] The mammary stroma also contains various cell types (e.g., immune cells and fat cells) that have the potential to influence tumor development, progression, and metastasis in humans and rodents.[108] Additionally, changes in the extracellular matrix composition can disrupt tissue organization, which is a step in malignant tumor progression.[109, 110]

Recent *in vitro*- and *in vivo*-based data suggest that breast cancer progression is the result of bidirectional signaling between nonepithelial, stromal components and malignant cells in the tumor

microenvironment. The stromal component demonstrates significant gene expression changes during tumor progression, which include genes controlling extracellular matrix composition and matrix remodeling. Epigenetic modifications in tumor-associated stroma also have been reported and are greater in HER2+ than in HER2– tumors.[111]

Stem/Progenitor Cells

Stem/progenitor cells have been identified in the human breast and rodent mammary gland. Mammary stem cells are thought to be the targets of cancer-initiating agents and the cell site where mammary cancers begin.[112, 113] One hypothesis proposes that, during proliferative expansion, stem/progenitor cells are sensitive to mutation by carcinogens. Because these cells are long lived and resistant to cell death, they are more likely to develop into neoplastic cells or tumors over time.[114] The cancer stem cell hypothesis therefore proposes that breast cancers are fueled by a subpopulation of cells that have the properties of self-renewal, tumorigenicity, and multilineage differentiation capacity.[115] This concept has implications for the potential role of environmental factors in breast cancer etiology and for cancer therapy.[116]

Inflammation

Although data are somewhat inconsistent, particularly in relation to breast cancer subtypes, epidemiologic studies suggest that inflammation may be another factor influencing the risk of breast cancer. For example, anti-inflammatory drugs are likely to reduce the risk of both ER+ and ER– breast cancer.[117-119] Human studies of breast cancer also have demonstrated that an inflammatory component contributes to tumor proliferation and metastasis.[120]

Anti-inflammatory drugs have been used in animal models for chemoprevention of mammary cancer.[121-124] As in human studies, animal models of breast cancer demonstrate that inflammatory processes contribute to tumor proliferation and metastasis.[125-128] Animal studies also have identified environmental chemicals that may impact the mammary gland by modulating inflammatory processes. For example, a study of rats found that prenatal exposure to BPA increased the expression of several pro-inflammatory cytokines and chemokines in female rats with abnormal mammary gland development.[129] Increased understanding of the origins and regulation of the inflammatory processes required for normal mammary gland development and their dysregulation in breast cancer can lead to innovative approaches for preventing and treating this disease.

Animal studies have provided some insight into the processes by which inflammation can promote mammary cancer. For example, the role of macrophages and eosinophils, cells involved in promoting inflammation, in normal pubertal mouse mammary gland development is well documented.[130] The role of inflammatory leukocytes (white blood cells) in mammary tumor progression also has been demonstrated in several animal models, highlighting the importance of the stromal environment and inflammatory components in promoting tumorigenesis.[131]

5.4.4 Gene-Environment Interactions and Susceptibility

Common genetic variants can affect associations between risk factors and disease, with some population subgroups likely to be more susceptible to environmental exposures than other subgroups. Distributions of genetic variants tend to cluster by continental ancestry, with prevalence of polymorphisms quite divergent between, for example, non-Hispanic Whites, Asians, and African-Americans.[132] Differences in susceptibility to environmental exposures may be due to variations in the way genes encode enzymes, which affects metabolism, DNA repair, and other pathways related to carcinogenesis. These gene-environment interactions were first observed in 1976 by Harris, who noted a 75-fold variation between individuals in the metabolic activation and binding of a carcinogen to human lung tissue.[133]

In the last decade, numerous human studies have examined gene-environment interactions and breast cancer. Studies have identified a possible

association between smoking, N-acetyltransferase 2 (NAT2) genotypes, and breast cancer.[134] NAT2 is involved in the detoxification and/or metabolic activation of some chemicals that individuals are exposed to in the environment, including carcinogens. Gene-environment interactions for smoking and breast cancer risk, however, still are being explored and findings to date are inconclusive. For example, a recent study examining large samples from the Breast and Prostate Cancer Cohort Consortium did not support the association between smoking, NAT2 genotype, and breast cancer found in earlier studies.[135] Other research on gene-environment interactions and breast cancer risk support the effects of genetic variability on associations between breast cancer risk and polychlorinated biphenyls (PCBs).[136] For instance, there now is some evidence that CYP1A1 (a gene upregulated following PCB/dioxin exposure) polymorphisms are linked to breast cancer risk, and recent work has specifically shown the polymorphic A2455G G allele to be a risk factor for breast cancer among Caucasian women.[137] In addition, women with BRCA mutations appear to be more vulnerable to early life exposures to radiation due to impaired gene repair mechanisms.[138,139] Pijpe and colleagues[140] also found that diagnostic radiation before age 30 was associated with a dose-dependent increase in breast cancer risk among women with BRCA mutations.

Differential distributions of common genetic variants by ancestry in humans may be comparable to various strains of rat and mouse, each with a different range of sensitivity to tumor induction.[13] For example, susceptible rat strains include the Sprague-Dawley, Wistar, and Lewis. Resistant rat strains are the Copenhagen and Wistar/Kyoto. Susceptible mouse strains include the BALB/c, FVB, and DBA2F, and a resistant mouse strain is the C57BL/6.[99, 141] Some mouse strains are not as effective as others for studying the role of the environment in mammary tumorigenesis.

An experimental animal model can be used to identify the part of the genome that contributes to risk for a disease. Testing is then performed to confirm that this part of the genome contributes to risk in humans. This comparative genomics approach was used by Gould[142] to identify breast cancer susceptibility genes that conferred a moderate risk of developing the disease. The investigators fine-mapped the specific location of mammary cancer genes (loci) on the rat chromosome and evaluated their comparable human gene homologs in breast cancer case-control association studies (studies that compare people with and without a specific disease).[143, 144] This approach yielded promising results, including the finding of compound rat quantitative trait loci (QTL), stretches of DNA containing or linked to the genes that underlie certain characteristics that vary in degree and can be attributed to multiple genes and their environment) and a nonprotein-coding mammary cancer susceptibility locus (Mcs5a/MCS5A) that modulates mammary cancer risk in rats and women. The gene locus Mcs5a acts after the initial step of transforming mammary epithelial cells in early cancer progression and also controls susceptibility through the immune system, independent of a contribution from mammary cells.[145]

Little is known about the mechanisms of mammary cancer susceptibility and resistance in mice. The resistant C57BL/6 strain is one of the two most commonly used genetic backgrounds for gene deletions in knockout mice (mice genetically engineered to have certain gene[s] inactivated). This hampers the interpretation of associations between gene modifications and tumor development because the C57BL/6 strain is highly resistant to mammary cancer development with or without gene modification.[12] Thus, to more correctly assess the impact of gene deletions, research needs to be conducted in a susceptible strain such as the BALB/c.

Novel rodent models show potential for revealing the mechanisms by which gene modifications affect breast cancer initiation, progression, and metastasis and interact with environmental factors in breast cancer. Many rodent strains are inbred, such that rats or mice of a given strain are largely equivalent to each other genetically. The genetics in the human population are heterogeneous, as are their responses to potential carcinogens, other environmental exposures,

and cancer treatments. Inbred rodent strains do not reflect the heterogeneity of human populations but are useful for examining possible mechanisms through which various environmental factors might influence breast cancer risk.[29, 48] Inbred rodent strains also have the advantage of helping to identify a subpopulation that is sensitive to a particular environmental factor. These inbred strains, therefore, offer the potential to accelerate the discovery of mechanistic end points as well as biomarkers of exposure to environmental factors. Scientists have developed strains of mice and, more recently, rats that express gene mutations (BRCA1, 2) and genetic variants (loss of tumor suppressor genes and overexpression of human oncogenes).[146, 147] In fact, specific strains that develop rare molecular subtypes of breast cancer now have been generated in the rat.[148]

5.5 Conclusion

In this chapter, we described background information that sets the foundation for the review of the state of the science in the next chapter. This chapter attempted to provide an understanding of several important issues, including:

- The animal-to-human research paradigm, which can accelerate research by optimizing the use of both controlled studies of animal models and various types of research in humans (e.g., epidemiologic and randomized clinical trials). Studies of animal models can be used to generate hypotheses for human studies as well as aid in the interpretation of the findings from human research. On the other hand, human studies generate questions that can be tested under controlled conditions with animal models, which have the advantage of allowing scientists to study the life span over a relatively short period of time. Integration of findings from both types of studies accelerates scientific knowledge and may improve the understanding of the applicability and limitations of animal models to human research. The multidirectional nature of animal and human research offers the application of the optimal system and study design for testing hypotheses and, therefore, should be used to examine the most important questions in future studies of breast cancer and the environment.

- The need to assess windows of susceptibility when exposures may have a greater effect on breast development and the risk for breast cancer. The timing of environmental exposures throughout a person's lifetime deserves greater attention in future research. In fact, this is a recommendation presented at the end of the next chapter (Chapter 6. State of the Science: Part 2).

- Breast/mammary gland development as a foundation for understanding breast cancer etiology. Data presented in this chapter on the timing of animal and human mammary gland development provide contextual information for the review of the literature on breast cancer and the environment in the next chapter.

- Potential mechanisms for carcinogenesis or enhanced tumor susceptibility that can individually or in combination contribute to the risk for breast cancer.

These important issues serve as background for the discussion of environmental risk factors for breast cancer throughout this report.

5

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6
CHAPTER

State of the Science: Part 2—Evidence From Animal and Human Studies and Cross-Cutting Themes

As specified by the Congressional legislation that established the IBCERCC, this chapter reviews research findings across disciplines that suggest environmental and genomic factors that may be related to the etiology of breast cancer. The chapter presents both animal and human evidence for the state of the science in breast cancer and the environment. It applies the animal-to-human paradigm to describe factors or exposures in two categories: (1) exposures that are recognized/accepted breast cancer risk factors; and (2) exposures that have some evidence linking them to breast cancer risk. The chapter also identifies important gaps in the evidence and recommends research for each risk factor. The chapter emphasizes the importance of transdisciplinary research and a life-course approach, which are described in detail in Section 6.3.1 together with relevant recommendations. Finally, the chapter identifies major research directions, makes recommendations to accelerate progress toward breast cancer prevention, and addresses policy implications. An outline of key research questions and related needs (Table 6.3) conclude the chapter.

6.1 Accepted Risk Factors for Breast Cancer Based on Human and Animal Data

Recognized or accepted risk factors are defined as factors for which there are confirmatory human data showing consistent associations between an exposure and cancer risk. Biologic plausibility and underlying mechanisms are often demonstrated by animal studies. The chapter, therefore, focuses on evidence from human studies but presents evidence from animal studies when appropriate and when recent animal research has made a significant contribution to the understanding of a particular risk factor. When both human and animal evidence are presented for a specific risk factor, human research is presented first, followed by the discussion of animal studies; each category of research is indicated by a subheading.

6.1.1 Family History of Breast Cancer

Aside from increasing age, one of the strongest known risk factors for a woman being diagnosed with breast cancer is having a first-degree female relative (i.e., mother, sister, or daughter) with a history of breast cancer. This association is correlated in most studies with a two-fold increase in risk,[1] Similarly, having a first degree relative with breast cancer increases risk for ER+, ER–/ PR–/HER2+, and triple negative (ER–/PR–/HER2–) breast cancer subtypes.[2] The proportion of women diagnosed with breast cancer who have a first degree relative with a history of the disease is between 10 and16 percent.[3] Although a proportion of this increased risk may be due to high-penetrance, low-prevalence (less common) genetic variants such as BRCA1 and BRCA2, combinations of more common, lower penetrance genetic variants confer small individual risk.[4,5] The link between breast cancer risk and having a first-degree female relative with a history of breast cancer may be due to a combination of genetic and shared environmental influences, including lifestyle.

Gaps

Scientists have limited information to explain why two or more family members expressing the same gene mutation are not affected equally by a disease. This statement is true for many diseases/cancers, not only breast cancer. The interactions of these gene mutations with endogenous hormones/growth factors and exogenous environmental factors are not known.

Recommendation

Investigate factors that influence the link between a family history of breast cancer and risk to better understand why women with the same mutation are not equally affected by disease. Also evaluate risk among families without mutations in rare, high-susceptibility genes. Factors requiring further investigation include (1) more common, lower penetrance genetic variants; (2) common lifestyle factors or environmental exposures (particularly early in life) that may explain differences in outcomes among women with the same mutation; and/or (3) epigenetic variations in DNA that are heritable but are not DNA mutations *per se*.

6.1.2 Rare and Common Genetic Variants

As noted above and reviewed by Hofstatter,[6] inherited mutations in the BRCA1 and BRCA2 genes confer a greatly increased risk of breast cancer, with individual lifetime risk estimates ranging from 26 to 85 percent. These mutations, however, are present in a small proportion of all women with breast cancer (5 to 10%) and do not account for the majority of cases among women with breast cancer in a first-degree relative. Other rare genetic variants associated with inherited cancer syndromes and increased breast cancer risk include PTEN, p53, CDH1, and STK11. These gene variants account for less than 1 percent of breast cancer cases.[7] Rare variants that confer more moderate risk of breast cancer include CHEK2, ATM, PALB2, and BR1P1.[8]

Genome-wide association studies (GWAS) compare groups of people with and without disease to identify differences in the distribution of genetic variations at hundreds of thousands of places across their genomes. GWAS have identified common genetic variations that confer a modest risk of breast cancer.[7]

Gaps

Thus far, GWAS have not accounted for all of the heritability of cancers found in family studies. It will be important to determine whether breast cancer risk and heritability can be explained more fully by investigating the interaction of low-penetrance loci with each other and with environmental factors or other genomic or epigenomic characteristics.

Information is limited regarding the contributions of common genetic variants to specific breast cancer subtypes, particularly in combination with environmental exposures. The role of gene-environment interactions over the life course in relation to the risk of breast cancer subtypes also is unknown. Advancing the understanding in these areas is exceedingly

important to develop appropriate, population-specific strategies for the prevention of all breast cancer.

Recommendations

- Support studies that identify rarer variants and other types of genomic characteristics (e.g., epigenomic factors) that may be associated with cancer risk. Studies also are needed to examine the degree to which low-penetrance loci interact with each other and with environmental factors to influence breast cancer risk.

- Support research in humans and animal models to investigate gene-environment interactions by specific breast cancer subtypes, among different subpopulations, and during different life stages. Research should examine whether gene variants are associated with all breast cancer subtypes or are specific to one subtype. Studies of genetic variants also could identify pathways that are targets for gene modification therapies for a small proportion of cancer patients.

6.1.3 Breast Density

Human Evidence

One of the strongest risk factors for breast cancer is breast density.[9] Breast density is a measure of the extent of epithelial and stromal components in the gland. The epithelial component is comprised of cells that line the lobules and terminal ducts. The stromal component, or stroma, is the connective tissue in the mammary gland/breast. The stroma, along with epithelial tissue, is what makes a breast appear dense on a mammogram. Breasts that have more fat tissue than stromal and epithelial components appear less dense on mammograms.

Studies have indicated a more than four-fold increased risk for breast cancer among women with very dense breasts compared to those with no mammographic densities.[10-13] This finding sets breast density apart from other risk factors. A recent study also found high breast density to be more strongly associated with ER– tumors, which have a poorer prognosis, relative to more common ER+ tumors.[14] In addition, high breast density was associated with more aggressive tumor characteristics and *in situ* tumors, but not with tumor histology, lymph node involvement, or PR and HER2 status.[14] Another study found that high breast density substantially increased risk for ER+, ER–/PR–/HER2+, and triple negative (ER–PR–/HER2–) breast cancer subtypes.[15] Breast density, however, has not been associated with reduced survival among breast cancer patients.[16, 17] Some evidence indicates that other factors may modify the risk conferred by high breast density. Recent research, for example, indicated that although low body mass index (BMI) is associated with premenopausal breast cancer, this association is attenuated after adjustment for breast density.[18] Breast density also can be altered by endogenous[19] and exogenous hormonal factors[20] as well as other factors such as age, parity, menopausal status, and BMI.[21]

The mechanistic basis for the association between breast density and breast cancer has not been defined, but a number of hypotheses have been proposed.[22] One hypothesis is that the number and proliferative state of epithelial cells may influence breast density and the probability of genetic damage that may give rise to cancer. Collagen and stromal matrix, which are products of stromal cells, may facilitate tumor development and invasion through their mechanical properties. Matrix metalloproteinases that regulate the stromal matrix also can regulate the activation of growth factors that might influence breast cancer susceptibility. Epithelial and stromal cell responses to environmental factors that change the prevalence and composition of these cells can contribute to differences in breast density. In addition, epithelial and stromal cell responses to environmental exposures may interact with hormones and growth factors to affect breast density.

Animal Evidence

To date, no experimental animal models have been developed to examine the link between breast density and breast cancer. Mouse and rat studies, however, have demonstrated that early life exposure to environmental factors such as dioxin,

perfluorooctanoic acid, and radiation can significantly alter the stromal component of the mammary gland.[23-25] For example, a link between mammary stroma-specific irradiation and increased prevalence of ER– mammary tumors with reduced latency has been reported in a p53-null mouse model (i.e., a mouse strain that lacks a functional p53 protein).[26, 27]

Gap

The reason(s) that breast density is a strong risk factor for breast cancer are not well understood. The role of breast density in the etiology of tumor subtypes and possible interactions with other risk factors also are poorly understood. In addition, evidence is needed to explain differences in breast density and the causes of those differences.

Recommendations

- Support studies of the mechanistic basis of breast density and its role in the etiology of tumor subtypes.

- Support studies that examine how breast density interacts with endogenous and exogenous environmental factors to increase breast cancer risk.

- Develop experimental models (rodent and cell-based) to investigate the role of breast density in breast cancer risk. Comparisons of breast samples from women and rodent models depicting the range and severity of density may accelerate research in this field of investigation.

6.1.4 Benign Breast Disease

Human Evidence

Benign breast disease encompasses a broad and heterogeneous range of conditions, many of which are not associated with breast cancer risk. Benign fibrocystic changes in the breast tissue include nonproliferative lesions, proliferative lesions without atypia, and proliferative lesions with atypia (atypical hyperplasia). Studies have shown that atypical ductal and lobular hyperplasia are the forms of benign breast disease that are most associated with an increased risk of breast cancer.[28] Lobular atypias, such as atypical lobular hyperplasia (ALH), are associated with a three- to four-fold increased breast cancer risk.[29] A history of atypical ductal hyperplasia (ADH) is associated with a four- to five-fold increase in risk.[30] Clinicians disagree on: (1) the probability that ALH, ADH, and ductal carcinoma *in situ* (DCIS), considered by some to be borderline lesions, will become malignant; and (2) the appropriate management of these lesions.[31] Recent analyses of genomic and transcriptomic alterations have provided insight into the relationship between ADH and DCIS and eventual invasive ductal carcinomas.[32] Comparative gene expression analyses support the concept that low-grade and high-grade DCIS arise from two distinct evolutionary pathways. ADH, low-grade DCIS, and low-grade invasive ductal carcinoma share nearly identical gene expression profiles associated with the ER+ phenotype. High-grade invasive ductal carcinoma and DCIS, on the other hand, are associated with triple negative breast cancer (TNBC).

Animal Evidence

Atypical hyperplasias have been shown to be precancerous in rats and mice. In mice, hyperplastic alveolar nodules (HANs) are the best-identified hyperplasia and give rise to ER–/PR– tumors.[33]

Ductal hyperplasias are the precursors of hormone-dependent mammary cancer in rats and humans. Whether a distinct hyperplasia gives rise to hormone-independent tumors in humans and rats is not known.

Gaps

Knowledge is lacking regarding the etiologic basis of ALH, ADH, DCIS, and low- versus high-grade tumor types. The influence of exposures to specific endogenous and exogenous factors at different life stages on the development of these conditions is unknown. In addition, little is known about differences in population subgroups with regard to the prevalence of different types of benign breast disease. With recent advances in the molecular characterization of breast lesions, epidemiologic and animal studies are poised to obtain data on the characteristics and life stage-specific exposures that predispose an individual to the development of different atypical breast lesions.

Recommendations

- Conduct research on the characteristics and life stage-specific exposures that predispose an individual to develop atypical breast lesions and that increase the risk of breast cancer subtypes from specific lesions. This research can help to identify susceptible populations (including age and racial/ethnic groups) that might be especially sensitive to exposures.

- Utilize animal models that develop specific breast lesions prior to invasive carcinoma to examine the effects of exposure to initiating agents at specific life stages on the development of specific types of lesions. The progression of lesions can be followed over time to assess the contribution of endogenous and exogenous environmental factors to invasive breast cancer development and progression.

6.1.5 Steroid Hormones and Reproductive Characteristics

Human Evidence

To date, the majority of accepted risk factors for breast cancer are related to a woman's lifetime exposure to circulating ovarian steroid hormones (estrogen and progesterone). In the early 1700s, Bernardino Ramazzini noted that breast cancer was more common among Catholic nuns than among married women, an observation now known to be attributable to not having children.[34] As reviewed by Key and colleagues,[35] risk factors related to an elevated lifetime exposure to hormones include early age at menarche, not having children, late age at first full-term pregnancy, and late age at menopause. These factors are thought to increase breast cancer risk by increasing the number of cycles of hormone-induced proliferation over the life span and the potential for errors in DNA replication during proliferation that lead to genetic instability and cancer-producing mutations.

A full-term pregnancy, especially before the age of 35 years, is thought to reduce risk through estrogen- and progesterone-induced differentiation of the mammary ductal epithelial cells, making them less susceptible to carcinogens.[36] The protective effect of parity on breast cancer risk appears to be limited to luminal subtypes, with an increased risk of ER– and/or basal-like breast cancer correlated with higher parity. Recent research also has found that a current or recent pregnancy may increase breast cancer risk, particularly among women in their 30s and 40s.[37] Investigators believe that the processes of immune suppression and tissue inflammation that naturally occur during involution may promote breast cancer. Conversely, having pre-eclampsia of pregnancy, a condition involving high blood pressure and other symptoms, is associated with a reduced risk of breast cancer in the mothers and the daughters of mothers with pre-eclampsia.[38]

Historically, researchers have focused on estrogen as the mediator of steroid hormone effects in the breast and breast cancer. Yet the greatest amount of proliferation in the normal human breast in cycling premenopausal women occurs during the luteal phase of the menstrual cycle, when levels of both progesterone and estrogen are elevated.[39] In the postmenopausal breast, the greatest amount of proliferation occurs in women receiving combined estrogen plus progestin hormonal therapy (HT) (compared with no HT and estrogen alone HT).[40] The Women's Health Initiative (WHI) Study demonstrated that combined estrogen plus progestin HT increased breast cancer risk compared with estrogen alone HT.[41] A decline in breast cancer incidence between 1999 and 2003, (principally in ER+ tumors in women ages 50 to 69)[42] was widely attributed to reductions in the use of combined HT.[43-45] Thus, the roles of progesterone and progestins in the etiology of breast cancer are suggested by the studies demonstrating that the greatest proliferation in the premenopausal breast occurs when both progesterone and estrogen levels are elevated. Findings from the WHI study also indicated that increased breast

> Historically, researchers have focused on the effects of estrogen on the breast. Studies such as the Women's Health Initiative, however, suggest that progesterone and progestins may have an important role in the etiology of breast cancer.

cancer risk only was associated with combined estrogen/progestin HT.

In utero exposure to synthetic hormones has been linked to breast cancer, as demonstrated by studies of individuals exposed to diethylstilbestrol (DES), a potent pharmaceutical estrogen used by millions of pregnant women between 1940 and the 1970s to prevent miscarriages.[46] Studies eventually revealed that *in utero* DES exposure of both male and female offspring increased neoplastic lesions of the reproductive tract and the incidence of benign reproductive problems. Women who were exposed *in utero* to DES had a significantly increased risk of breast cancer. Their mothers also experienced an increased risk of breast cancer.[47, 48] Importantly, the highest risks were correlated with the highest cumulative doses of DES during pregnancy.[49]

Animal Evidence

The same reproductive factors linking ovarian steroid hormones and breast cancer in humans are operative in the development of mammary cancers in rodents. For example, ovariectomy (surgical removal of ovaries) reduces mammary tumor development in all animal models.[50, 51] Increased susceptibility of the mammary gland to environmental effects during the peripubertal period and pregnancy, the protective effect of early pregnancy, and the increased breast cancer risk associated with recent pregnancy observed in humans also are observed in the mouse and rat.[52, 53] The protective effect of early pregnancy in rats and mice is thought to be due to a number of factors, including: (1) induction of differentiation; (2) removal of damaged cells during lactational involution; and (3) permanent changes in receptor levels and response to hormones in cells remaining after involution. Lyons and colleagues,[53] however, identified mammary gland involution as a driver of tumor progression in a mouse model of postpartum breast cancer. This study further found that inflammatory processes were involved in tumor progression in the involuting mammary gland. Analyses of the effect of hormones in pre- versus postmenopausal states also have been performed in rats. Studies of ovariectomized rats (surrogate for the postmenopausal state) treated with either estradiol alone or estrogen plus progestin revealed a higher incidence and higher degree of aggressiveness of ER+PR+ mammary cancers in the estrogen plus progestin treated rats.[54] The same studies have revealed the signaling pathways mediated by estrogen plus progestin and suggest novel treatments targeting these pathways in ER+PR+ breast cancers.

Animal studies provide the largest body of evidence regarding the mechanisms by which exogenous hormones may affect mammary cancer. Studies of mice treated with estradiol early in life show that advanced epithelial growth of mammary tissue does not occur until they reach adulthood. In fact, duct growth has been reported as inhibited early in life but accelerated after puberty. This accelerated development after estradiol exposure is correlated with a greater number of undifferentiated terminal end buds (TEBs). In early adulthood, TEBs in control animals differentiated as expected, whereas TEBs in estradiol-treated mice remained, making the animal more susceptible to neoplastic lesions later in life.[55] Ethinyl estradiol, the predominant estrogen in oral contraceptives, also has been shown in a multigenerational rat study to induce significant hyperplasia in male mammary tissue for more than two generations.[56] Male mammary gland hyperplasia was reported to be the most sensitive end point evaluated in multiple studies.[57]

The effect of early exposure to DES on breast cancer risk has been demonstrated in rodents. Early life DES exposure in mice induced greater outgrowth of the mammary gland ducts around the time of puberty, dilated mammary ducts at 12 weeks of age, resulted in precocious lactation, and increased mammary tumor incidence as adults. Exposure to DES during windows of susceptibility also increased mammary tumorigenesis in Syrian golden hamsters and rats treated with the carcinogen dimethylbenz-a-anthracene (DMBA). In those studies, DES increased the number of mammary tumors, numbers of tumors per rat, and the severity of tumor malignancy. These findings suggest that, in addition to being carcinogenic alone, DES increases the sensitivity of the mammary gland to other carcinogens.[58, 59]

Rodent studies have demonstrated the latent effects of prenatal exposure to other hormones, such as testosterone. Studies that exposed rats to testosterone prenatally found that the female offspring had regressed nipple development (i.e., masculinized mammary morphology), leaving them unable to nurse their own offspring. Early postnatal treatment of mice with testosterone stimulated ductal branching in the mammary gland around the time of puberty.[55] Other animal studies have linked testosterone to mammary cancer. For example, a study of transgenic rats with an overexpression of the neu oncogene in the mammary gland found that males developed androgen-dependent mammary cancer and females developed mammary cancer only when treated with testosterone.[60]

Animal studies also lend support to findings from human studies implicating progesterone and progestins in the development of breast cancer. For example, exposure of mice to the progestin medroxyprogesterone acetate (MPA), widely used in combined menopausal HT, has been shown to induce a high incidence (80%) of ER+PR+ mammary cancers.[61] Another study supporting the role of progestins in mammary cancer development found that two antiprogesterone compounds (ZK98.486 and RU 486) inhibited tumor development in ovary-intact rodents in the MXT mouse tumor model and both DMBA- and MNU-induced mammary tumors in rats.[62]

Gaps

Evidence is lacking regarding the reasons for the differential effect of parity on breast cancer subtypes. The role of hormonal exposures over the life course in the etiology of breast cancer subtypes also is poorly understood and requires further research.

Given that progesterone and progestins are implicated in breast cancer etiology, research is needed to understand the underlying mechanisms of their effects. More evidence also is needed to elucidate the potential contribution of exogenous environmental factors to increased progesterone levels and implications for different population subgroups.

Hormonal compounds other than DES, particularly off-label progestins, now are being given to pregnant women to prevent miscarriage. The risks of these current hormonal treatments to pregnant women and their children, particularly with regard to breast cancer, are not known but may be of concern. The effects of hormone-based contraceptives in their various compositions and dosing schedules also are not well understood in relation to life stage susceptibility to breast cancer.

Limited research has been conducted to understand the etiology of male breast cancer. Scientists lack information on the effects of hormones on male breast development, the potential for gynecomastia, and their relationship with later breast cancer risk.

More research is needed to understand the protumorigenic effect of postpartum involution.

Recommendations

- Support research to identify the underlying mechanisms that regulate steroid hormone action across life stages in the normal breast and in breast cancer. These projects should consider different breast cancer subtypes and include but not be limited to: (1) evaluation of progestin and estrogen-mediated effects; (2) examination of newly described estrogen receptors in breast development and function; and (3) evaluation of the ability of exogenous chemical influences to disrupt normal steroid (e.g., progesterone, estrogen, and androgen) signaling. Of particular relevance are studies to gain a more complete understanding of the putative effects of endogenous and exogenous hormones on the regulation of normal breast stem cells and the eventual development of tumors.

- In particular, support research that examines differences in the pre- and postmenopausal breast that lead to variable sensitivity to exogenous steroids. Research also must explore the underlying pathways that explain specific differences in pre- and postmenopausal breast cancer. In addition, epidemiologic research should address whether stages of breast development occur at

- a different pace among women at high risk for premenopausal breast cancer compared to those at risk for postmenopausal breast cancer. These studies also should investigate further the mechanisms that underlie the protective effect of parity. In addition, studies must investigate the mechanisms underlying breast cancer that are associated with postpartum involution.

  Animal research can use ovariectomized animal models as surrogates for the postmenopausal stage and compare them to non-ovariectomized animal models to identify potential reasons for differences in the etiology of pre- versus postmenopausal mammary cancer and explore periods in the life course when the mechanisms occur.

- Support studies to evaluate interactions between pharmaceutical hormones and endogenous factors and/or other exogenous environmental influences across different life/developmental stages, including pregnancy. Animal- and cell-based assessment of pharmaceuticals (e.g., birth control, HT, hormones for pregnant women) can be used to examine potential health effects of these agents. These studies should collect and evaluate mammary gland samples in rodents or different types of mammary cells cultured under specific physiological conditions.

- Update postmarket surveillance or observational studies on both mothers and their offspring for effects that follow changes in dosing regimens or formulations of hormones used in birth control pills and off-label hormones taken by pregnant women.

- Support studies of the effect of exogenous hormones on male breast development, the potential for gynecomastia, and their relationship with later breast cancer risk.

6.1.6 Physical Activity

Human Evidence

Sufficient evidence exists to conclude that physical activity reduces the risk of breast cancer by 20 to 40 percent.[63, 64] A 2004 meta-analysis of the effects of physical activity during adolescent and young adult years indicated an overall reduction in the risk for breast cancer of 21 percent among the group in the highest category of physical activity compared to those in the lowest category, with a similar magnitude estimated from case-control and cohort studies as well as by menopausal status.[65] Subsequent meta-analyses indicate some evidence, albeit inconsistent, for the benefits of physical activity on breast cancer survival,[66-68] with the suggestion of greater benefit among specific population subgroups.[69] Furthermore, energy expenditure of African American women and girls may be much lower than non-Hispanic White peers when engaged in the same physical activity in controlled laboratories, indicating that the effects of physical activity interventions may differ for women by racial/ethnic group.[70] Comparisons of studies of physical activity and breast cancer risk and survival are complicated by the fact that very different measures of physical activity may be used across studies. Substantial advances, however, have been made in the measurement of physical activity for population surveillance.[71]

Animal Evidence

The animal data suggest a mixed response to physical activity with regard to mammary tumor multiplicity and burden. In adult p53-deficient MMTV-Wnt-1 transgenic mice that form spontaneous mammary tumors, the animals that engaged in the most physical activity demonstrated shorter survival times than controls by 10 to 13 weeks. The group with the highest level of exercise had increased multiplicity of mammary carcinomas compared to nonexercise controls. All exercising animals weighed less than their respective controls.[72] This unexpected, negative effect of exercise might be due to other factors, such as variations in the fitness of different litters of mice that were exposed to the different levels of exercise. Conversely, in rats, pubertal physical activity reduced mammary epithelial targets for neoplastic transformation through epithelial differentiation. This physical activity also upregulated tumor suppressor genes BRCA1, p53, and ERβ, and reduced the ERα/ERβ ratio in the rat mammary

gland.[73] Without information about the comparability of exercise in the transgenic mice to human physical activity patterns, it is difficult to assess the implications of these findings.[72]

Gaps

The pathways associated with and the mechanisms that mediate the protective effects of physical activity on breast cancer risk need to be elucidated, including potential interactions with genetic and other non-genetic factors. This would aid in developing intervention strategies in population subgroups at the highest risk for breast cancer.

Little evidence is available about associations between physical activity and breast cancer subtypes. The influence of physical activity at various life stages and its impact on pre- versus postmenopausal cancer risk also are not well understood.

Life course evaluation of exercise habits and overall physical activity is difficult to establish, which has led to a gap in knowledge about physical activity at various life stages and its impact on breast cancer outcomes.

Recommendations

- Support human and animal studies that examine the mechanisms by which physical activity affects breast cancer risk in general and for specific subtypes. These studies should examine the differential effects of physical activity on pre- and postmenopausal breast cancer and consider interactions with genetic and other nongenetic factors.

- Support studies of physical activity and breast cancer that focus on specific population subgroups, such as racial and ethnic groups, with differential energy expenditure who are at increased risk of breast cancer in general or a subtype.

- Support the development of novel methods for evaluating physical activity across the life course during specific life stages (e.g., during puberty). Novel methods of recording or recalling this information are needed to move this field forward.

6.1.7 Alcohol Consumption

Human Evidence

Alcohol intake is a recognized risk factor for breast cancer. Based on an analysis of 53 epidemiologic studies involving 58,515 women with invasive breast cancer and 95,067 female controls, Hamajima and colleagues[74] reported that, compared with women who reported not drinking alcohol, the relative risk of breast cancer was 1.32 for an intake of 35 to 44 grams per day of alcohol and 1.46 for an intake of at least 45 grams per day. The relative risk of breast cancer increased by 7.1 percent for each additional 10 grams per day intake of alcohol (i.e., for each extra alcoholic drink consumed per day). The increased risk of breast cancer with increased alcohol intake was the same in ever-smokers and never-smokers.[74] This finding provides additional support for the association between alcohol consumption and breast cancer. The results of the Hamajima study were confirmed by numerous studies showing that consumption of alcohol, even at moderate doses, increases the risk of breast cancer, particularly for ER+/PR+ subtypes.[75] The specific mechanism linking alcohol consumption to breast cancer risk in humans has not been identified, but there is speculation that estrogen metabolism may be modified. Data from the Nurses' Health Study further suggest that low levels of alcohol consumption in both early and later life are associated with increased breast cancer risk. In this study, a cohort of 105,986 women was followed from 1980 until 2008 as they completed an early adult alcohol assessment and eight updated alcohol assessments.[76] This study is one of the first to examine alcohol intake across the adult years and associated risk for breast cancer.

Animal Evidence

Alcohol consumption also increases mammary cancer development in rodents. Proposed mechanisms in mice include: (1) pro-inflammatory mechanisms that promote tumor angiogenesis; and (2) an estrogen signaling pathway that results in increased systemic estrogen levels.[77] In rats, maternal alcohol intake during pregnancy increased mammary tumorigenesis in female offspring, possibly as a result of alcohol

exposure causing persistent alterations in mammary gland morphology, enhanced ER-alpha, or increased circulating estradiol levels.[78]

Gaps

Although some evidence suggests that alcohol consumption is primarily associated with ER+ breast cancer, relationships between alcohol consumption and breast cancer subtypes have not been investigated thoroughly. Data also are lacking on alcohol and breast cancer risk among population subgroups, and on interactions with alcohol intake and genetic and other environmental factors, such as diet.

Knowledge is lacking regarding the relationship between alcohol exposure and breast cancer risk at different life stages, as well as the effects of different levels of alcohol exposure on breast cancer risk.

Recommendations

- Support research to understand the underlying mechanism(s) that link alcohol intake to risk for breast cancer and its subtypes, as well as the specific interactions of alcohol exposure, genetics, and other environmental factors, such as diet, that may modify these risks.

- Support research within specific population subgroups (e.g., smokers) and across the life span to examine the relationship between alcohol exposure and breast cancer and its subtypes.

- Support research to elucidate the relationship between alcohol exposure at different life stages (e.g., *in utero*, puberty) and both pre- and postmenopausal breast cancer. Consider the effects of different levels of exposure at different life stages.

6.1.8 Radiation Exposure

Human Evidence

Radiation exposure has been shown to confer a relatively large increased risk for breast cancer. Radiation exposure resulting from the atomic bombings of Hiroshima and Nagasaki has been associated with an increased breast cancer risk, particularly if exposures occurred during adolescent years.[1, 79, 80] Diagnostic and/or therapeutic radiation to the breast area (e.g., for Hodgkin disease, tuberculosis, scoliosis) has been shown to increase breast cancer risk more than four-fold, especially if this treatment occurs before age 30.[81] In addition to young women, certain subgroups of people appear to be more genetically susceptible to radiation, such as persons with chromosome instability disorders (disorders involving the gain or loss of whole chromosomes or fractions of chromosomes), and hereditary syndromes, such as retinoblastoma.[81]

Findings demonstrate that the relationship between radiation exposure and breast cancer in humans is important given the increasing use of diagnostic imaging tests involving radiation. The dose of radiation per person in the United States increased 600 percent between the early 1980s and 2006.[82] A major contributor to this increase is the 20-fold increase in the annual number of computed tomographic (CT) scans.[82, 83] More than 70 million CT scans were performed in 2010.[84] The proportion of individuals who received what is considered high and very high annual radiation exposures also may have doubled between 1996 and 2010, according to an analysis of six large integrated health systems.[85] Repeated scans expose people to cumulative radiation doses that are at levels associated with increased cancer risk.[81] In addition, children receiving CT scans are likely to experience greater cancer risks because of the higher cumulative lifetime doses received and a greater number of remaining years of life during which cancers may form.[86] Children also are more sensitive to radiation than adults are and, as a result, the cancer risk at any given dose of radiation is higher for children than adults.[87] A report estimated that 29,000 new incident cancers will occur in the future due to radiation exposures from CT scans performed in 2007.[88] In an attempt to reduce harm from inappropriate use of tests involving radiation, a consortium of members of relevant professional societies formed the Alliance for Radiation Safety in Pediatric Imaging and launched the

Image Gently campaign.[a] The U.S. Food and Drug Administration (FDA) also launched an Initiative to Reduce Unnecessary Radiation Exposure.[b] These initiatives promote appropriate imaging, aim to increase patient awareness, and take other steps to help ensure that imaging studies are justified (i.e., expected to do more good than harm) and optimized to use the least amount of radiation required for appropriate image quality.

Animal Evidence

Studies in rats also have found a link between irradiation and mammary cancer and lend support to the findings in humans suggesting windows of susceptibility in early life. For example, studies have found that immature rats are significantly more susceptible to mammary cancer induction by radiation.[89] Rat studies further show interactions between irradiation and chemical carcinogens as well as irradiation and estrogenic hormones (such as those used in contraceptives) that increase mammary cancer risk. Rodent studies may provide a relevant experimental system in which to investigate interactions between radiation and other environmental factors and their effect on mammary cancer risk.

Studies in mice have shown that irradiation causes aggressive mammary tumors through a variety of mechanisms.

Irradiation likely induces mutational effects as a result of DNA double-strand breaks (severing of both strands of a chromosomes' DNA). Recent studies in mice have revealed that irradiation exposure restricted to mammary stroma, without irradiation of mammary epithelium, causes accelerated development of aggressive mammary tumors and a shift to a predominance of ER– tumors. These effects of irradiation are due to an altered stromal microenvironment that results in the combined activation of TGFβ, extracellular matrix remodeling, and deregulation of mammary stem cells. These effects are distinct from radiation effects on genomic integrity[27] and reveal novel mechanisms by which irradiation influences breast cancer risk.

Gaps

Although definitive evidence exists demonstrating that radiation exposure at a young age is a risk factor for breast cancer, the work is not finished in this area. For example, evidence is lacking on the interaction of different kinds of radiation exposures over the life course, interactions between these exposures and genetic and other environmental factors, and their impact on breast cancer risk.

Although it is clear that moderate to high doses of ionizing radiation can cause breast cancer in girls and young women, questions remain regarding the effects of cumulative exposure to low-dose radiation, such as diagnostic radiologic exams.[85]

New methods also are needed to protect children from damaging radiation exposure and to track cumulative radiation exposure over time.

Recommendations

- Support research to identify the effects of different radiation modalities (e.g., CT scans, fluoroscopy) on breast development and the risk for breast cancer and its subtypes in humans and animal models. This research should focus on the identification of underlying mechanisms and methods for prevention, as well as potential interactions of radiation with genetic and nongenetic factors.

- Support efforts to track cumulative individual radiation exposure through various modes (e.g., CT scans, fluoroscopy, mammography, interventional radiology, and radiotherapies) using computerized medical records and other methods.

- Support additional research on the effects of low-dose radiation exposure, particularly in girls and young women. Research on low-dose radiation

[a] www.imagegently.org
[b] http://www.fda.gov/Radiation-EmittingProducts/RadiationSafety/RadiationDoseReduction/default.htm.

- also should examine the best model for predicting breast cancer risk from low-dose exposures. A commonly used model employs linear extrapolation from higher doses to directly estimate risk at low doses of radiation (linear no-threshold model). Other models exist that predict no risk (threshold mode), less risk (linear quadratic mode), or a beneficial effect (hormesis hypothesis) from low doses of radiation.[87] The linear model often is used in part because of its conservative risk prediction.

- Support research to develop methods for protecting children from damaging radiation exposure. Medical devices that emit radiation should be monitored to ensure that machines are calibrated to radiation doses that provide optimal imaging at minimal exposures. These calibrations should take into consideration age, body mass, and other individual characteristics that could lead to overexposure to radiation. Research also is needed to validate the use of nonradiation-based breast cancer imaging.

6.1.9 Adult Body Mass Index, Weight Gain, and Height

Human Evidence

A pooled analysis of data from large, prospective cohort studies demonstrated that high BMI (BMI > 25 kg/m^2) is a recognized risk factor for postmenopausal breast cancer, presumably because adipose (fat) tissue is a site for aromatization of androgens to estrogens. Conversely, in the same analysis, very high BMI (BMI > 31) was associated with reduced risk for premenopausal breast cancer.[90]

Weight gain in adult years is associated with increased risk for postmenopausal breast cancer and reduced risk for premenopausal breast cancer.[91] In a meta-analysis of the association between adult weight gain and breast cancer risk by receptor status, risk for both ER+PR+ and ER– tumors was elevated with increasing weight gain during adulthood up to the age at diagnosis of breast cancer, with the risk higher for postmenopausal breast cancer than for premenopausal breast cancer. Risk from weight gain in adulthood was higher for postmenopausal diagnosis of ER–PR– tumors, but not for ER–PR+ tumors. In addition, being obese (BMI > 30 kg/m^2) at the age of diagnosis, regardless of menopausal status, confers poorer survival.[92] Finally, being tall is a risk factor for postmenopausal breast cancer in the pooled analysis of prospective cohort data[90, 92] and for premenopausal breast cancer in the analysis of the Million Women Study.[93]

Animal Evidence

Studies in animal models have consistently demonstrated that obesity increases mammary cancer development. Many possible mechanisms and pathways may be involved in the association between obesity and mammary cancer, including those involving insulin-like growth factor-1 (IGF-1), insulin resistance, leptin, adiponectin, inflammation, and steroid hormones, among other factors.[94, 95]

Postmenopausal obesity has been modeled in rats that differ in their predisposition for obesity following consumption of a high-fat diet. Pubertal rats were treated with a carcinogen and placed on an obesogenic diet (diet designed to induce obesity). In adulthood, the rats were separated into lean, midweight, and obese rats based upon weight gain and then ovariectomized. Regression of hormone-dependent tumors was less in the obese than in the lean or midweight rats, and tumors in the obese rats had more ER+ cells. Investigators hypothesized that reduced energetic efficiency and increased mammary fat cell aromatase activity and estrogen production might be the potential basis for the effect found in obese rats.[96]

In animal models of breast cancer subtypes, mammary tumor development and progression in MMTV-Wnt-1 transgenic mice, an established model of basal-like breast cancer, was enhanced by diet-induced obesity and suppressed by calorie restriction. In contrast, whereas calorie restriction suppressed tumor formation in MMTV-neu transgenic mice, an established model of Luminal B breast cancer, diet-induced obesity had no effect. Neither calorie restriction nor diet-induced obesity influenced mammary tumor development in C3(1)-T-antigen transgenic mice, a model of TNBC.[97]

A variety of mouse models consistently demonstrate increased mammary tumorigenesis in animals fed a high-fat diet without the confounding effects of obesity. For example, a high-fat diet can increase the numbers of HER2/neu mammary tumors with little weight gain.[98] Fatless A-Zip/F-1 mice show increased mammary tumorigenesis associated with development of insulin resistance and expression of many inflammatory products that promote tumor progression.[94, 99] Studies also found that a high-fat diet can enhance mammary tumorigenesis in MMTV-TGF-alpha mice without obesity.[100] Diet-induced obesity in mice also has been associated with inflammation and elevated aromatase expression in the mammary gland, which can promote cancer development.[101] These mouse model studies primarily examined the effect of diet on ER– tumors, the predominant mammary tumor type in mice.

Gaps and Recommendations

See General Gaps and Recommendations for BMI, weight, and diet at the end of Section 6.2.1.

6.2 Risk Factors With Some Evidence for Breast Cancer Based on Human and Animal Data

This section discusses risk factors with some evidence to support their relationship to breast cancer based on either animal or human research or both. Data supporting these relationships are not consistent, but these factors represent emerging areas of research that are likely to be important to the primary prevention of breast cancer. When both human and animal evidence are presented for a specific risk factor, human research is presented first, followed by the discussion of animal studies. Each category of research is indicated by a subheading.

6.2.1 Diet, BMI, and Weight Throughout Life

Research on body size and diet has been conducted in many developmental periods of the life course. In adults, these risk factors have been investigated extensively. Known risk factors related to adult BMI, weight gain, and height were discussed in Section 6.1.9. The topics in this section represent areas for which the evidence is less conclusive. The gaps and recommendations at the end of this section, however, relate to adult, adolescent, and childhood weight and diet because many of these gaps and recommendations are relevant across the life course. In addition, scientists have not been able to fully separate the influences of diet and body size on breast cancer risk at this point in time. A single gap and recommendation, therefore, can relate to both weight and diet.

Although this discussion of weight and diet is not included in the Accepted Risk Factors section, a fair amount of animal and human research supports the relationship between some factors discussed in this section and breast cancer risk. For example, several studies illustrate the important role of body size in early breast development.

Weight in Early Life

Although little evidence exists to support a direct relationship between weight throughout most of childhood and breast cancer risk (see the section on BMI in Puberty for a discussion of evidence supporting an indirect relationship), a growing body of evidence supports a link between birth weight and breast cancer risk. A large meta-analysis found that women whose birth weights were 8.5 pounds or greater had an increased risk of breast cancer compared to lower birth weight women.[102] This finding confirmed previous research that found associations between higher birth weight and breast cancer.[38]

Diet in Early Life

Evidence is building that diet and obesity in pregnancy and during early life may influence mammary carcinogenesis and breast cancer risk. Most of this evidence, however, has been obtained through animal studies.

Animal studies have demonstrated that maternal diet and health have major effects on fetal development.

Assessing the effect of dietary changes on developing mammary glands is an important end point that has been well studied in rodent models. Maternal rodent diets high in n-6 polyunsaturated fatty acids (PUFAs) increased mammary fat pad size in female offspring, the amount of epithelium throughout the gland during puberty, and the density of TEBs. In contrast, a maternal diet high in n-3 PUFAs slowed mammary gland development and ductal growth in offspring. Upon exposure to a mammary carcinogen, mice whose mothers were fed a high n-3 PUFA diet in pregnancy had fewer mammary tumors and took a longer time to form tumors. Mice whose mothers were fed a high n-6 PUFA diet in pregnancy had more tumors and experienced a shorter time to tumor development.[103] These findings demonstrate the importance of understanding the effect of fat composition in the maternal diet on breast cancer risk over the life course of the offspring.

Studies in rats indicate that the timing of dietary fat exposure may be important. Rats fed a high-fat diet during the peripubertal period (post-weaning to puberty) had higher body weight and mass, advanced vaginal opening, and subtle modification in mammary gland morphology, suggesting that the effect of increased body weight on pubertal maturation is similar to that in humans.[104] In addition, rats exposed *in utero* and during puberty to high levels of various dietary fats (39% vs. 16% of kcal) reflecting popular fats in Western diets (olive oil, safflower butter compared to reference soy oil) all showed enriched mammary gland expression of cell cycle genes and increased mammary gland proliferation during puberty.[105] No assessment of dietary fat exposures on body weight or pubertal maturation was reported in this study. In a subsequent study, those on the high-fat diet had reduced tumor latency and increased incidence, which was especially true for corn oil-based diets and less so for olive oil-based diets.[106] Rats were exposed to a high-fat diet with 40 percent energy from safflower oil at different periods of the life course, including either *in utero*, postnatally, at puberty, early adulthood, late adulthood, or for their whole life beginning *in utero*. Mammary tumor incidence was significantly higher in the *in utero* (60%), adulthood (61%), and whole-life (91%) exposure groups compared to the unexposed group (32%). The puberty and adult groups both demonstrated a 44 percent incidence of mammary tumors.

BMI in Puberty

Human Evidence

BMI in humans before adulthood is a key breast cancer research area. Prepubertal overweight and obesity are at the forefront of suspected contributors to early puberty.[107] Data from the Centers for Disease Control and Prevention (CDC) in 2011 show that 17 percent (12.5 million) of U.S. children and adolescents ages 2 to 19 years are obese, defined as being over the 95th percentile in BMI for their age.[108, 109] Childhood obesity has been associated with early pubertal development.[110] The pioneering work of Herman-Giddens and colleagues raised the possibility of a link between increasing rates of obesity and the trend toward early puberty.[111] Recent studies by the Breast Cancer and the Environment Research Program (BCERP), however, suggest that other environmental components, such as dietary phytoestrogens and chemicals, also may be involved in the trend toward early puberty.[112] Various mechanisms have been proposed to explain the association between obesity and altered pubertal timing, including increased levels of circulating estrogens in obese girls and/or increased aromatase activity in breast fat resulting in increased conversion of local or systemic androgens to estrogens. Both mechanisms would result in greater exposure of breast tissues to estrogen during prepubertal years.[113] The relationship between earlier breast developmental timing and breast cancer risk, however, is not known.

Animal Evidence

Studies on the effects of body weight on mouse mammary gland development show that the timing of dietary exposures during specific mammary gland developmental stages and genetic backgrounds (strain differences) determine the effects of dietary fat on body weight and the mammary gland.[114] Pubertal Balb/c mice failed to gain more weight on a diet high in animal fat but experienced a stimulatory

effect on mammary gland development. In contrast, pubertal C57BL/6 mice gained weight on the same high-fat diet but experienced an inhibitory effect on mammary gland development. Neither strain, however, demonstrated a significant effect of the high-fat diet on weight gain or on mammary gland morphology when the high-fat diet was given in adulthood. The underlying mechanisms for these findings have yet to be determined and may not relate to the relationship between BMI in the human peripubertal period and pubertal maturation and breast development. Nevertheless, the observation that a high-fat diet can impact mammary gland development without causing overweight or obesity suggests that, in a heterogeneous human population, dietary fat may affect a much broader population than those who experience significant weight gain or obesity.

Dietary Intake in Adulthood and Breast Cancer

In 2007, the American Institute for Cancer Research and the World Cancer Research Fund convened an expert panel to review the evidence for "Food, Nutrition, Physical Activity, and Prevention of Cancer: A Global Perspective." The panel report included a summary of the peer-reviewed literature and concluded that there was limited but suggestive evidence of an association between dietary fat intake and risk for postmenopausal breast cancer. Findings were inconsistent for other foods and nutrients evaluated, and the report lists the evidence as "limited—no conclusion" for fruits and vegetables, fiber, soy, dairy, meats, and specific foods, nutrients, and micronutrients. Lack of associations between dietary factors and breast cancer risk could be the result of numerous sources of bias, including misclassification of dietary intake. Furthermore, the time period in which diet may play the most important role is unclear. Food frequency questionnaire data usually reflect diet during the year prior to diagnosis or in adulthood prior to breast cancer. In addition, as noted above, the lack of consideration of breast tumor subtypes in the analysis of associations could result in null findings if specific factors increase the risk of one but not other subtypes. More recent research from the Multiethnic Cohort Study (MEC), a prospective study of 85,089 postmenopausal women with 3,885 incident invasive breast cancer cases, did not support an association between breast cancer and adult intake of total fat—saturated or other specific types of dietary fat, including individual fatty acids.[115] These findings did not vary by ethnicity, estrogen/progesterone receptor status, tumor stage, BMI, hormone replacement therapy use, follow-up period, family history of breast cancer, or smoking status at baseline.

Phytoestrogens

Phytoestrogens are naturally occurring compounds found in plants that have estrogenic activities. An increased focus on healthier lifestyles usually entails lower fat intake, increased consumption of vegetables, and often adding supplements to the diet that are high in phytoestrogens.

Human Evidence

The effects of developmental exposure to genistein, one of the most abundant and bioactive compounds in soy, have been studied because many U.S. infants are fed soy formula during their first year of life.[116,117] Human studies suggest a modest inverse association between soy food consumption and breast cancer risk.[118,119] Epidemiologic studies further indicate that childhood/peripubertal exposure to soy components provides protection against breast cancer later in life.[120,121] A recent meta-analysis of prospective studies in soy and breast cancer indicated that soy intake reduces breast cancer incidence and recurrence,[122] as observed in an earlier report of case-control studies.[123] Findings were significant for postmenopausal but not premenopausal women. Strong associations appeared for women in Asian but not Western countries, which might be explained by the much greater amount and extent of soy consumption over the life course in Asia.

Animal Evidence

Genistein has variable effects on the development of both mouse and rat mammary glands depending on timing, dose, and route of exposure.[117] The effect of genistein exposure on mammary cancer susceptibility also seems to depend on the timing of exposure.

Accelerated mammary development was seen in two rat studies that included 5 days of postnatal exposure. TEBs differentiated into mature structures earlier than in controls, and a decreased risk of developing mammary cancer was noted.[124, 125] One of these studies observed a decrease in the multiplicity of tumors in rats treated with genistein,[124] and the other noted a significant increase in the density of lobulo-alveolar structures, which correlated with a decreased susceptibility to chemical carcinogen challenge.[125] Conversely, a study of neonatally exposed mouse mammary tissue showed slowed growth and altered timing of the appearance and numbers of ERs, a situation generally thought to increase tumor risk.[116] Other studies in mice and rats found an increased risk of mammary tumorigenesis following prenatal genistein exposure, with accelerated development of TEBs and decreased differentiation with age, indicating a longer period for potential TEB exposure to environmental toxins. The rat studies further demonstrated that offspring exposed to genistein prenatally had an increased incidence of mammary tumors when they also received a mammary gland carcinogen.[124, 126]

Other animal studies indicate that exposure to genistein during the prenatal period may increase mammary cancer risk, particularly in males. In a multigenerational reproductive study conducted by the National Toxicology Program and National Center for Toxicology Research, rats received dietary genistein during *in utero*/prenatal development and into adulthood. Abnormalities in both male and female mammary glands were demonstrated, with changes in peripubertal males being most apparent.[56, 127] Clear evidence of hyperplasia also was found in the male rat mammary gland for at least two generations following either developmental ethinyl estradiol or genistein exposures. This finding indicates that the male rat mammary gland is sensitive to endocrine disruption by different types of estrogens, including phytoestrogens. The mammary gland in the male rat, therefore, can be used to detect endocrine disruption related to estrogen exposure.[56]

Dietary Patterns

Human Evidence

A meta-analysis of dietary patterns and breast cancer in 2010 found a modest (11%) decrease in breast cancer risk in the highest compared to the lowest categories of a prudent/healthy dietary pattern (healthy pattern defined as high in fruits, vegetables, and whole grains and low in fat) in both case-control and cohort studies as well as cohort studies alone.[128] The authors discussed the potential for bias of both a differential and nondifferential nature and called for additional research, as it is well known that foods and nutrients are not eaten in isolation but as part of a dietary pattern. Since the meta-analysis by Brennan and colleagues in 2010, Zhang and colleagues reported that Chinese women in the highest quartile of the vegetable-fruit-soy-milk-poultry-fish consumption pattern (prudent) had a decreased risk of breast cancer compared to those in the lowest quartile. Women following the refined grain-meat-pickle diet (Western) also had a more than 2.58-fold increased breast cancer risk.[129] An Australian cohort study further found that high consumption of fruit and salad was associated with a reduced risk of breast cancer for ER–/PR– cancers and a marginally reduced risk for ER+/PR+ cases.[130] Two articles from the United Kingdom Women's Cohort Study also described an inverse association between a fish-eating dietary pattern and breast cancer risk, but no association between breast cancer risk and the Mediterranean or the World Healthy Diet Index.[131] The French EPIC study cohort, however, found that the alcohol/Western diet was directly associated with a risk of ER+/PR+ breast cancer, whereas the healthy/Mediterranean diet was inversely associated with a risk of ER–/PR– cancer.[132] A German study, on the other hand, found none of these associations.[133]

Some human studies have examined caloric restriction as a dietary pattern. The evidence supporting a relationship between caloric restriction and breast cancer risk, however, is inconsistent. The lack of consistent

findings may be explained by extreme stress and other circumstances that have accompanied severe caloric restriction in human populations (e.g., the Dutch Famine of 1944, Norwegians during World War II). Stress and other factors related to food deprivation may have separate and independent influences on cancer risk in affected populations.[95]

Animal Evidence

Studies of dietary patterns comparable to those examined in human studies have not been conducted in animal models *per se*. Different oils/fats reflecting various types of diets, however, have been tested in animals. For example, a DMBA challenge assay study found that rats fed a diet high in corn oil tended to exhibit accelerated pubertal timing and increased tumor susceptibility compared to rats fed a diet high in olive oil.[104, 106] Studies in animal models also have consistently found that caloric restriction decreases mammary cancer development.[94, 95]

General Gaps for Diet, BMI, and Weight

The dietary studies described in this section were selected to illustrate research on dietary macronutrients, components, and patterns related to breast cancer risk, particularly where human data are not conclusive but animal data are convincing. The role of diet during different life stages in breast development and breast cancer or breast cancer subtype risk has not been examined well. In addition, the potential underlying mechanisms by which diet might influence breast cancer have not been identified in either humans or animal models. A major limitation to this body of research is the tendency to focus on the effects of one macro- and micronutrient at a time rather than on the whole diet or dietary patterns. The populations studied also have not had sufficient heterogeneity in dietary intake to be able to detect an association. In addition, studies have not been conducted to assess the relationship between dietary patterns and exposures to environmental contaminants from soil, water, air, and food additives. Similarly, many diet-related studies are not adjusted for other relevant lifestyle factors, such as BMI or physical activity.

Research is lacking with regard to pre- versus postmenopausal BMI effects on the risk for breast cancer and breast cancer subtypes. Research also is needed to examine the influence of weight change and interactions with endogenous and exogenous factors across the life span, including the body burden of environmental contaminants.

Conflicting findings between animal and human studies point to the difficulties in reconciling data in transdisciplinary research and the need to further refine our measures and study methods to improve the accuracy of risk assessment. For example, using BMI as a marker for obesity is problematic because no analog exists in animals. There are, however, methods for assessing body composition and amount of fat in animal models. Animals studies of diet also have limitations in their application to humans because animal and human diets differ extraordinarily, thereby reducing the ability to unravel underlying mechanisms that link diet to breast cancer.

Research is needed on how BMI affects the body burden of environmental contaminants and on the association between environmental contaminants in adipose tissue and breast cancer risk. In addition, scientists lack a clear understanding of the underlying mechanisms for the effects of BMI on breast cancer or mammary tumorigenesis by menopausal state.

General Recommendations for Diet, BMI, and Weight

- Support research on life stage-specific evaluations of food additives or biologically active food components (as a part of the whole diet), especially those shown to alter reproductive end points, to determine their effects on breast development and tumor risk by breast cancer subtype. Both direct (e.g., artificial flavors and colors, preservatives) and indirect (e.g., components of packaging) food additives should be evaluated and interpreted, as dietary intake of processed foods changes over the life course.

- Support research in animals and humans on the role of diet and other environmental exposures on breast development and cancer risk in

- populations with adequate variation in dietary intake, with an emphasis on life stage-specific exposure assessments and their relationship to breast cancer subtypes.

- Support research on the mechanisms underlying the relationship between BMI and breast cancer risk by menopausal status as well as the mechanisms underpinning the role of weight change on cancer risk. Additional research is needed on the interactions between endogenous factors, such as hormones, and exogenous environmental factors on breast cancer risk by subtype across the life span.

- Support the development and refinement of measures and methods in animal studies of diet and weight that will allow these studies to better inform research in humans.

6.2.2 Inflammation

Human Evidence

Epidemiologic studies indicate that anti-inflammatory drugs may reduce the risk of both receptor-positive and receptor-negative breast cancer.[134-136] These findings suggest that inflammation has a role in breast cancer etiology. Both human and animal studies of breast cancer have demonstrated that an inflammatory component contributes to tumor proliferation and metastasis.[137]

Animal Evidence

Anti-inflammatory drugs have been used in animal models for chemoprevention of mammary cancer.[138-141] In addition, the role of macrophages and eosinophils in normal pubertal mammary gland development and mammary tumor progression in mice is well documented.[142, 143] Ductal elongation requires that macrophages interact with the TEBS, and eosinophils are required for proper ductal development, particularly branching. These two cell types, therefore, perform complementary roles in pubertal mammary gland development. Recently, mast cells also have been implicated in pubertal mammary gland ductal morphogenesis, with a role independent of that of macrophages.[144]

Several studies using animal models of breast cancer have demonstrated that inflammatory processes contribute to tumor proliferation and metastasis.[143, 145-147] Environmental exposures that increase inflammatory processes in the mammary gland, such as a diet high in saturated fat, are known to promote mammary cancer. Other environmental exposures may impact the mammary gland through the modulation of inflammatory processes. For example, prenatal exposure to bisphenol A (BPA), an endocrine disruptor, was reported to increase the expression of several pro-inflammatory cytokines and chemokines in rats.[148]

Gaps

Scientists lack knowledge about the types of endogenous and exogenous factors that cause and/or modulate inflammation in the breast, which inflammatory factors are involved, and the potential role of inflammation in the development of breast tumor subtypes or specific population subgroups. Knowledge gaps include the identification of molecular targets for the alleviation of inflammation, the time of life when inflammation may play a critical role in breast cancer development, and if and at what life stage anti-inflammatory drugs and other health behaviors that may reduce inflammation can decrease breast cancer risk.

An increased understanding of the origins and regulation of the inflammatory processes required for normal mammary gland development and their dysregulation in breast cancer is needed and can lead to innovative approaches for preventing and treating this disease.

Recommendations

- Support research on endogenous and exogenous factors that cause or promote inflammatory processes in the breast and increase the overall risk of breast cancer and specific subtypes of the disease. This research also should examine specific population subgroups that exhibit higher rates of breast cancer subtypes and/or might be more susceptible to inflammation due to endogenous and/or exogenous factors.

- Support investigations of the role of inflammation due to environmental exposures during windows of susceptibility, the role of anti-inflammatory drugs in reducing breast cancer risk during these periods, and molecular targets to reduce breast inflammation.

- Support research to determine the origins of the inflammatory process in the mammary gland and its dysregulation in breast cancer to advance knowledge about when and how inflammation can be avoided or reduced to prevent breast cancer.

6.2.3 Light at Night (LAN)/Melatonin

Human Evidence

Shift work was declared a probable human carcinogen in 2007 by the International Agency for Research on Cancer (IARC). It has been hypothesized that disruption of circadian rhythm, particularly through night shift work or "light at night" (LAN), suppresses melatonin and may be associated with breast cancer risk.[149, 150] Although findings obtained since the IARC report are mixed, as reviewed by G. Costa, Haus, and Stevens,[151] six of nine studies of shift work reported associations with a moderate increase in breast cancer risk. Results from laboratory studies in rats additionally demonstrated that nighttime exposure to artificial light increased the growth of breast tumors by suppressing melatonin.[152] Of four studies since the IARC report that assessed the association between LAN or shift work and breast cancer risk, Q. Li and colleagues[153] found an increased breast cancer risk in women who were exposed to artificial light in a domestic setting, and Kloog and colleagues (2011)[154] found a 30 to 50 percent increased risk of breast cancer from higher LAN compared to lower LAN. Pesch and colleagues[155] also reported an association between long-term night work and an increased breast cancer risk.

Animal Evidence

In a review of the effects of melatonin on mammary tumor burden in rats, melatonin supplementation: (1) increased tumor latency (the time elapsing between the administration of the carcinogen and the appearance of palpable mammary tumors); (2) significantly reduced tumor incidence (the percentage of animals that developed tumors); (3) reduced the number and size of tumors; (4) increased the incidence of benign fibroadenomas relative to adenocarcinomas; and (5) increased spontaneous tumor regression.[156] In C3H/Jax mice, known for a high incidence of spontaneous mammary tumors, prolonged oral melatonin treatment significantly reduced the development of mammary tumors[157, 158] Melatonin treatment of MMTV-c-Neu mice also significantly reduced the incidence of preneoplastic lesions as well as the incidence of adenocarcinomas.[159] In transgenic mice expressing the *c-neu* breast cancer oncogene under the control of an MMTV promoter, melatonin delayed the appearance of palpable tumors and the growth of the tumors.[160]

Gaps

Although moderate evidence in both humans and rodent models supports the effects of both melatonin and LAN on breast cancer risk, more research is needed to understand the mechanisms and pathways associated with these effects and develop approaches to alleviate the effects of shift work on cancer risk. Studies also are needed to examine time periods in the life course when LAN has the greatest influence on the risk of breast cancer.

Recommendations

- Support research on the mechanisms that underlie the melatonin/LAN and breast cancer association to identify preventive strategies for night-shift workers. Additional research in existing or new cohorts of shift workers could answer some of the epidemiologic questions. Both human and animal studies to identify and then use biomarkers to better understand the underlying mechanisms should be conducted.

- Support research to identify windows of susceptibility when LAN might have a greater impact on the risk for breast cancer and specific subtypes.

6.2.4 Protein Hormones and Growth Factors

Human Evidence

In addition to steroid hormones, numerous other protein hormones and growth factors have been shown to be associated with breast cancer risk. These endogenous compounds are characterized as endocrine, paracrine, or autocrine factors that play pivotal roles in mammary growth or function, or participate in a signal cascade required for normal growth/function. Large-scale pooled analyses of prospective studies have demonstrated a positive association between the ratio of estradiol, free estradiol, and other estrogens as well as testosterone and risk of postmenopausal breast cancer[161] over time.[162] These findings suggest that it may be important to understand the relationship between different hormones during the life stages, and these ratios may depend on enzyme activities that convert steroids from an inactive to an active form following environmental influences. An inverse association between sex hormone binding globulin (SHBG), the protein carrier for steroid hormones, and breast cancer risk in the aforementioned pooled analysis also has been demonstrated consistently.[162] SHBG levels are inversely correlated with BMI and, therefore, are a marker for leanness of women and the potential for less aromatization of hormones from androgens to estrogens. Studies with smaller sample sizes have not demonstrated necessarily the same associations.

A hormone that is elevated in obesity is leptin, which is a protein hormone derived from fat cells, and it has been associated with carcinogenesis as well as increased tumor migration and invasion, angiogenesis, and aromatase activity.[163] Research on the association between leptin and breast cancer risk has produced inconsistent results but suggests that leptin may be a risk modifier. Another hormone that merits consideration with regard to breast cancer risk is prolactin. Prolactin is an endocrine hormone produced in the pituitary that has a primary role in milk production during lactation. There is a dramatic drop in prolactin after lactation under normal circumstances, and prolactin is a difficult hormone to measure reliably. Prolactin has been correlated with breast cancer risk in some large epidemiologic studies but not in others.

Although hormones are rarely measured in the breast microenvironment of breast cancer patients and controls, a recent article reported higher concentrations of estrogens and androgens in the breast and serum of ER+/PR+ patients compared to ER–/PR– patients.[164] Other receptors for growth factors are measured in tissues by immunohistochemistry and may be used to describe the tumor subtype, such as the epidermal growth factor (EGF) family receptors EGFR and erbB2 or HER2. HER2 plays a role in normal breast development, and its overexpression is an indicator of poor prognosis in breast cancer.[165]

Animal Evidence

The discussion of breast cancer etiology in Chapter 5 provides more information about the role of protein hormones and growth factors in breast cancer, including evidence from animal studies.

Gaps

Scientists do not know how chemicals, particularly endocrine-disrupting compounds (EDCs; see Section 6.2.6 for a discussion of these compounds), interact with endogenous hormones that are known to affect breast growth and proliferation.

Current understanding of the effects of certain endogenous hormones, such as leptin, on breast development and cancer risk is inadequate.

In addition, the effects of endogenous hormones on male breast development and breast cancer risk are poorly understood.

Recommendations

- Support research to examine how EDCs interact with endogenous hormones that are known to affect breast growth and proliferation and increase breast cancer risk.

- Support research to assess whether leptin and other hormones are associated with breast cancer risk overall, breast cancer subtypes, and breast cancer in different population subgroups.

- Support studies to understand the mechanisms of male breast cancer and the role of endogenous hormones. Further followup of existing cohorts should focus on male breast cancer to evaluate relationships between endogenous hormones and the risk of breast cancer among men.

6.2.5 Psychosocial Factors

Human Evidence

Social, cultural, and psychosocial factors influence the risk of breast cancer. These factors can exert a direct influence on breast cancer risk, for example, through increased exposure to environmental hazards in low-income areas. These factors also can have an indirect effect on breast cancer risk by creating stressors that ameliorate or enhance the impact of chemical, physical, and lifestyle and behavioral factors that influence this risk. These influences are dynamic and occur throughout the life course.

Low-income communities often face greater exposure to urban air pollution as well as chemicals and pesticides that have been implicated in both pre- and postmenopausal breast cancer.

Low-income communities often face greater exposure to urban air pollution as well as chemicals and pesticides that have been implicated in both pre- and postmenopausal breast cancer (see Section 6.2.6 on Chemical Exposures). One study found higher levels of several toxins in the homes of residents in a low socioeconomic status (SES), largely Hispanic community that borders an oil refinery relative to levels in a higher SES and majority White coastal community in the same region.[166] The effect of environmental exposures on breast cancer risk, however, could not be ascertained in this community. A recent study that characterized population disparities in exposure to BPA and polyfluoroalkyl chemicals (PFCs) found higher levels among individuals with lower compared to higher family income.[167]

Characteristics of the built environment (human-made or modified surroundings[168]), such as buildings, parks or green space, water supply, roads, or energy sources in neighborhoods and cities, also may influence pubertal onset[169] and breast cancer risk through their effects on lifestyle, behavioral factors, and environmental exposures.[170] Features of socioeconomically deprived neighborhoods may limit access to and inhibit physical activity. These neighborhoods also tend to have fewer stores containing fresh fruits and vegetables and more fast food restaurants and liquor stores, which may lead to unhealthy diets and greater BMI.[171-173]

Some argue that living in low-income and minority communities that often have high exposure to environmental hazards also increases stress through crowding, social disorganization, racial discrimination, and economic deprivation.[174] People in these communities face a greater risk of psychological stress, which can make them more vulnerable to the health effects of environmental hazards.[175]

Psychosocial factors, such as stress, influence pubertal development in girls[176] and breast cancer risk directly.[177] Stressful family environment and maternal depression have been linked to early pubertal maturation.[178] The absence of a biological father also has been associated with early puberty, including earlier menarche (a risk factor for breast cancer discussed earlier in this chapter)[179, 180] and breast development.[181] Research also suggests that stressful life events may be associated with breast cancer, even after controlling for other risk factors such as BMI, alcohol use, smoking, and physical activity.[182] Researchers have found a positive association between exposure to one or more stressful life events and risk of breast cancer.[183] Meta-analyses on the topic, however, have found only modest associations between life stressors and breast cancer risk.[184] Mechanisms for these associations may include: (1) changes in immunologic function; (2) hormonal

triggers; (3) modified cellular response to environmental factors; and (4) altered sleep patterns and eating habits. Overall, evidence demonstrates the need for further large-scale studies on the relationship between stress and breast cancer.

Animal Evidence

Experimental models are beginning to explore the effect of psychosocial environments on mammary carcinogenesis. For example, animal models have shown that social isolation increases the size, number, distribution, and malignancy of spontaneous mammary gland tumors.[185] Epidemiologic evidence supports this finding by indicating that social isolation of the neighborhood environment may be associated with breast cancer risk.[186]

Gaps

Research on the effects of psychosocial factors and breast cancer risk is challenging, as these factors often change throughout the life course. Research has established that one's neighborhood can increase the risk of lifestyle behaviors and conditions associated with breast cancer risk, such as obesity. Knowledge is lacking, however, about the processes and pathways by which the neighborhood environment, an individual's perception of the environment, and lifestyle characteristics make a person more susceptible to the effects of environmental contaminants that may influence breast cancer risk.

Knowledge is lacking regarding the mechanisms that underlie the contribution of larger-scale societal factors to inequitable patterns of exposures and breast cancer risk. These factors need to be assessed and taken into account in the design of future studies of breast cancer and the environment.

Recommendations

- Support studies that examine psychosocial risk factors across the life course and develop improved methods for identifying and measuring these risk factors.
- Support research that increases our knowledge about the mechanisms that underlie the contribution of larger scale societal factors to inequitable patterns of environmental exposures, susceptibility to the effects of environmental exposures, and breast cancer risk.

6.2.6 Chemical Exposures

More than 84,000 synthetic chemicals are registered by the U.S. Environmental Protection Agency (EPA) for commercial use and only 1 to 2 percent have been tested in rodent models by the National Toxicology Program (NTP) and other organizations for carcinogenicity.[187, 188] More than 2,000 chemicals have been tested for health-related effects and, according to an extensive literature search by Rudel and colleagues, 216 of those (slightly more than 10%) were found to affect mammary tissue.[187] In Rudel's review, a chemical was designated as a carcinogen if at least one study linked it to significantly increased mammary gland tumors and it was found in one of the following sources: the University of California, Berkeley's Carcinogenic Potency Database (CPDB), IARC Monograph Summaries, NTP Technical Reports and 11th Report on Carcinogens, and Chemical Carcinogenesis Research Information System (CCRIS).[89, 187]

The EPA has more than 84,000 chemicals registered for commercial use. Less than 2 percent of these chemicals have been tested to determine if they might cause breast cancer.

This section provides an overview of evidence describing the relationship of chemicals to breast cancer risk. Separate discussions are provided for EDCs and chemical carcinogens. The structure of this section differs slightly from earlier sections in this chapter because the main findings are summarized in tables (with more detail provided in appendices). Animal (*in vivo* and *in vitro*) and human epidemiology research findings are separated in the tables but not in the text. The text is intended to provide a

summary of important findings in the field and provide background for the information in the tables.

Chemical Carcinogens

Laboratory animal, *in vitro*, and human breast cancer studies support the conclusion that nonhormonal chemical carcinogens can play a role in human breast cancer. Examinations of the mutation patterns in the p53 tumor suppressor gene in breast cancer indicate that racial and geographic differences in the types of mutations found might be due to heritable and environmental factors.[189-192] In laboratory animals, numerous chemical carcinogen models of breast cancer are available.[193] Studies also show that chemical carcinogens can reach the breast in laboratory animals and humans because they are lipophilic and may be stored in the adipose tissue of the breast.[100, 194] Ductal epithelial cells are directly exposed to nicotine[195] and mutagenic compounds.[196] Heterocyclic amines, formed when meat is cooked at high temperatures and is well-done, also are present in tobacco smoke. When these amines were administered to nursing rat dams, high levels of the amines were found in the breast tissue of the dams, and the amines were excreted in the milk.[197] Other lines of evidence indicate that breast tissues

Table 6.1. Examples of chemical carcinogens affecting the breast

(See Appendix 3 for more detail and references on these chemicals.)

Chemical (listed alphabetically)	Properties and Uses	Animal Study Findings (*in vivo, in vitro*)	Human Exposure and Health Effects
Aryl Aromatic Amines	• Present in tobacco smoke and synthetic fuels	• Some aryl aromatic amines may be mutagenic and carcinogenic to human breast cells • Induces mammary tumor formation in rodents	• Exposure from mainstream and passive tobacco smoke and metabolic reduction of polycyclic nitroaromatic hydrocarbons (ubiquitous in diesel exhaust and in airborne particulates) • Pooled and meta-analyses showed increased risk with smoking for women with slow N-acetyltransferase (detoxifies aromatic amines) genotypes
Heterocyclic Amines (HAAs)	• Formed when meat is cooked • Present in tobacco smoke	• Some are powerful mammary carcinogens in rodents	• A 2010 meta-analysis demonstrated a 17% increase in the odds of breast cancer determined by meat intake (31 epidemiologic studies represented)
N-Nitrosamines	• Mutagenic compounds	• Induce rodent mammary tumors that are histologically similar to human cancers and can metastasize • Transform cultured mouse mammary cells • Cause cultured human mammary epithelial cells to undergo unscheduled DNA synthesis	• Exposure through diet, endogenous formation in the stomach, tobacco smoke, occupation, rubber products, and medical therapies • Have been detected in pacifiers and baby bottle nipples • No studies
Polycyclic Aromatic Hydrocarbons (PAHs) (MIXTURE)	• Formed from incomplete combustion of hydrocarbons	• Induce mammary tumors in laboratory rats	• Pervasive in the environment • Presence of PAH-DNA adducts is associated with breast cancer risk in the Long Island Breast Cancer Project • Associations between PAHs and breast cancer risk could be restricted to subgroups of women with high-risk genotypes
Tobacco Smoke (MIXTURE)	• Cigarettes contain about 3,600 chemicals	• Of more than 60 known carcinogens in tobacco smoke, several are known to induce mammary tumors in laboratory animals	• Affects the metabolism and/or mutagenicity of hormones and/or other carcinogens in breast tissue • Human studies demonstrate that tobacco constituents can reach breast tissue • The Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk declared that both active and passive smoke exposure increase breast cancer risk • The Nurses' Health Study confirmed that active smoking in women, especially prior to having their first child, increases breast cancer risk

can metabolically activate chemical carcinogens and increase the biologically effective dose. DNA adducts have been identified in normal breast tissue from women with and without breast cancer,[198-200] some of which were putatively related to tobacco smoking. These findings demonstrate that the breast certainly is exposed to chemical carcinogens and can be susceptible to the carcinogenic process.

Gaps

Studies are needed to examine chemicals both as carcinogens—acting directly to enhance breast tumor risk—as well as modifiers of breast cancer susceptibility and breast development.

Of the vast majority of chemicals available on the market, only a small percentage have been tested for health effects, and an even smaller percentage have been evaluated for effects on the mammary gland. Knowledge is especially limited about the effect of mixtures of chemicals, which reduces the ability to define the most important chemical influences for evaluation in human populations.

Studies of human populations often lack exposure information, except for the time just before or after breast cancer diagnosis. Animal data have proven that exposures at different stages of breast development might influence cancer risk; thus, exposure assessment needs to be conducted much earlier than the diagnosis. Most chemical carcinogens have not been tested for effects during early life, when windows of susceptibility are known to exist, or during adolescence or early adulthood.

Evidence is lacking regarding the effects of chemicals on breast cancer subtypes and on breast cancer in males.

Evidence is lacking on how overall health, other exposures, and genetic predisposition influence the response to chemicals.

Research is lacking on factors that may modulate or protect against adverse effects of environmental toxicants on the breast.

Recommendations

- Support chemical testing that includes evaluating carcinogenicity and promoter activity that increases breast cancer risk. Support research to evaluate life stage-specific effects of a full range of exposures when evaluating chemicals for carcinogenicity in rodent studies.

- Support research that focuses on enhanced testing of chemicals, especially classes of chemicals combined together as a mixture, for effects on the mammary gland and breast using susceptibility models relevant to tumor subtypes that are predominant in women. The identified chemicals or their mixtures then should be examined for potential epigenetic and genetic effects.

- Prioritize human studies that evaluate pubertal timing, growth indices, and environmental exposure information across the life course as well as store serum/urine samples to facilitate the assessment of breast cancer risk in adulthood.

- Conduct surveillance to identify chemicals that demonstrate a capacity for carcinogenicity or promoter activity with regular monitoring in the home, workplace, neighborhood, and from biospecimens in humans. Develop biomonitoring surveillance systems for those environmental chemicals already identified as promoters or that influence breast cancer risk.

- Advance the examination of altered development in males and females, including lactation impairment, hyperplasia, and dysplasia in academic, industry, and government chemical screening studies in rodents. All of these outcomes should be considered to be adverse effects of exposure to an individual or mixture of environmental factor(s). Assess the potential role of different forms of altered development in the etiology of mammary gland/breast cancer and its subtypes.

- Evaluate how overall health, other exposures, and genetic predisposition may interact with different exposures to influence mammary gland/breast

- development as well as mammary/breast cancer and its subtypes.

- Conduct research on factors that may modulate or protect against adverse effects of environmental toxicants.

Endocrine-Disrupting Compounds

Besides their effects as classic carcinogens, several classes of chemicals have demonstrated adverse effects on mammary gland development and subsequent susceptibility to chemical carcinogens. These EDCs interfere with the synthesis, secretion, transport, binding, action, or elimination of endogenous, natural hormones in the body that are responsible for development, behavior, fertility, and maintenance of homeostasis (normal cell metabolism). Identified EDCs that act on the breast include phytoestrogens, plastic additives, and pesticides, among others that were reviewed recently.[52, 57, 201] People commonly are exposed to a large number of EDCs as a mixture, and exposures appear to differ by life stage. Some compounds are so common that 95 percent of the participants across age groups in the National Health and Nutrition Examination Survey (NHANES) biomonitoring project had been exposed to them (e.g., PFOA, benzophenone-3, and methyl paraben).[202] These individuals, however, likely were exposed to different doses of specific EDCs, and dose is a critical variable in assessing

Table 6.2. Examples of endocrine-disrupting compounds affecting the breast

(See Appendix 3 for more detail and references on these EDCs.)[c]

Endocrine Disruptor (listed alphabetically)	Properties and Uses	Animal Study Findings (*in vivo, in vitro*)	Human Exposure and Health Effects
2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)	• Industrial incineration and chemical reaction-dependent pollutant • Bioaccumulative, lipophilic contaminant • Binds the aryl hydrocarbon receptor (AhR) • Known carcinogen	• Increased mammary tumor incidence and shorter latency in female rats exposed to carcinogen during development • Alters pubertal end points in rodents, including delayed mammary gland development in multiple rat strains	• Slowed breast development in the highest exposed girls in two countries • Suggestive data for breast cancer from industrial accident in Seveso, Italy, not conclusive • Increased breast cancer risk in Hamburg cohort
Atrazine	• One of the most heavily used herbicides on food and grain crops in the United States • Unknown mode of action in mammary tissue	• Causes early onset of mammary tumors and an increased incidence of tumors in specific rat strains • Alters pubertal timing in rodents • Promotes mammary tumor proliferation in rodent models • Impairs the development of mammary tissue and lactational ability in rats • Accelerates reproductive senescence	• Ecologic data for well water and breast cancer risk • Declared not relevant for breast tumorigenesis in humans by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel[203]
Bisphenol A (BPA)	• A component of polycarbonate plastics and epoxy resins • Large production volume • Leaches into food through food container linings • Found in dental sealants and composites • "Weak" estrogen	• Binds to nuclear ER-α and β • Activates the membrane-bound form of the ER (ncmER), estrogen-related receptor gamma (ERR-γ), GPR30, and AhR; possible thyroid hormone and androgen receptor interaction • Induces hyperplastic lesions in mammary tissue of prenatally exposed mice and rats at doses that approach human exposures • Alters the growth of the non-human primate mammary gland • Increases susceptibility to carcinogen-induced mammary tumors in rodents	• No studies, but widespread human exposure

[c] A large amount of information on pesticides is included in this section because much work has occurred in this area. EPA has helped to accelerate the knowledge of potential health effects of pesticides by requiring testing before they are marketed.

Table 6.2. (continued)

Endocrine Disruptor (listed alphabetically)	Properties and Uses	Animal Study Findings (*in vivo, in vitro*)	Human Exposure and Health Effects
Dichlorodiphenyl-trichloroethane (DDT) (MIXTURE)	• Insecticide that controls insect-borne disease • Degrades to p,p′-DDE, the most prevalent and persistent metabolite in the environment	• DDT and metabolites are known to exhibit anti-androgenic and estrogenic activity • Limited evidence for the chemical acting as a promoter of mammary tumors in rats	• Use peaked in the United States in 1959 • Banned by EPA in 1972 • No associations in pooled and meta-analyses evaluating serum adult levels; one study showing early life exposure associated with increased breast cancer risk in women
Dieldrin	• Persistent agricultural pesticide	• Causes increased tumor burden in HER2/neu transgenic mice exposed during pregnancy and lactation	• Used in the United States from the 1950s to 1970s; U.S. ban in 1987 • One prospective study showed a positive association with breast cancer risk
Metals	• Naturally occurring, they mimic or perturb normal hormonal milieu	• Cadmium can alter mammary development in mice and rats with low levels of prenatal exposure, mimicking estrogen	• Exposure through water, air, and cigarette smoking • Higher urinary cadmium levels in women were associated with a Breast Imaging-Reporting and Data Systems (BI-RADS®) density category of "extremely dense"
Nonylphenol	• Found in the lining of food containers and wraps, cleaning compounds, and spermicides • Known to have estrogenic properties	• Induces a dose-dependent increase in mammary cell proliferation, mammary epithelial branching and budding, and hastened differentiation in prenatally exposed female rats • Produces DNA mutations and chromosomal abnormalities, with increased tumor risk	• No studies
Perfluorooctanoic Acid (PFOA)	• Possesses long half-life in humans (2 to 4 years) and mice • Used in fire-fighting foams, electronics, and to make products that are grease- and water-proof • Final degradation product of other >8-carbon perfluorinated materials	• Effects on mammary glands of mice include altered development, altered lactation, obesity in young adults (developmental exposure), and changes in gene expression • Delays mammary gland development and obesity at body burdens that overlap with human exposure burden in contaminated parts of the United States	• Delayed pubertal timing in girls • Low-powered case-control study of Greenlandic Inuit women demonstrated significant correlation of serum perfluorinated chemicals and breast cancer risk
Phthalates	• Used to soften plastics for medical tubing and children's toys • Disperses or retains scent in health/beauty products	• Abnormal mammary alveolar branching and hypoplasia in perinatally exposed female rats • Retained nipples in perinatally exposed adolescent male rats • Dilation of mammary alveolar buds and ducts in adult male rats • N-butyl benzyl phthalate (BBP) increased the proliferative index of TEBs and altered the genomic profile of weanling rats	• Widespread environmental contamination has been found in human infants following critical care procedures • One study showed increased breast cancer risk in a Northern Mexico cohort of women with the highest phthalate burden
Polybrominated Diphenyl Ether (PBDE) (MIXTURE)	• Widely used to retard fire ignition time in textiles, construction materials, and polymers used in electronics • Bioaccumulative and lipophilic compound	• Altered reproductive end points in rodents, delayed mammary gland development, and thyroid hormone and behavioral alterations • Effects on breast cancer risk not yet assessed	• No studies

Table 6.2. (continued)

Endocrine Disruptor (listed alphabetically)	Properties and Uses	Animal Study Findings (*in vivo*, *in vitro*)	Human Exposure and Health Effects
Polychlorinated Biphenyls (PCBs) (MIXTURE)	• Mixed set of organochlorine isomers • Bioaccumulate in the body • Varying modes of action—some estrogenic, androgenic, or dioxin-like	• Affect pubertal end points in rodents • Possible mutant p53 interaction	• Known exposures from fish and milk • Majority of studies null; several studies suggest that high PCB levels and CYP1A1 genotypes may interact to increase breast cancer risk • Declared "possibly carcinogenic" to humans by IARC/EPA • Affects pubertal end points in girls

the effects on health outcomes. Numerous studies have generated critical novel data indicating that chemicals do not have to act as carcinogens (i.e., initiating tumorigenesis), but may have an effect on the breast that simply makes it more susceptible to another adverse influence, such as a different chemical or carcinogen. Many EDCs may fall into this category.

Gaps

Large gaps continue to exist in the understanding of breast cancer risk due to endocrine-disrupting chemicals. Although a number of EDCs are known to adversely affect the lifetime risk of mammary tumor development, current chemical test guidelines are not adequate to assess the effects of environmental chemicals on the mammary gland. In fact, many government and industry chemical testing studies do not require evaluation of the mammary gland. Where individual chemicals have been identified as contributing to mammary tumorigenesis in animal models, consistency is lacking with regard to study design, evaluation methods, and determination of the mechanisms of action for a given chemical. Chemical screening studies in rodents frequently fail to consider altered mammary development in males and females (permanent changes to mammary gland morphology, cell populations, hormone response, and gene expression), lactation impairment, and mammary hyperplasia and dysplasia (potential precursors to neoplasia) as adverse effects.

Evidence is lacking with regard to the effects of different levels of exposure. EDCs may have effects on humans at low doses (i.e., in the range of typical human exposures or effects observed at doses below those used for traditional toxicologic studies) that cannot be predicted by higher dose effects.[204]

Recommendations

- Improve animal and *in vitro* assessment of chemicals/pharmaceuticals/food additives for potential health effects by specifically *requiring* the collection and evaluation of mammary gland samples in testing for industry and government health evaluations. Develop and implement consistent chemical-testing protocols to be used across agencies and industry.

- Support research in human populations to assess the effects of EDCs on breast cancer risk, intermediate biomarkers related to breast cancer (such as estrogen levels in biospecimens from humans), and health conditions and developmental milestones related to breast cancer risk, such as puberty across a range of exposure levels and across the lifespan.

- Test the effects of different doses of EDCs in animal and human studies to identify levels that are related to the risk of breast cancer-related events and thus define the exposure-risk relationship.

6.2.7 Tobacco Smoke

In the past, evidence for an association between smoking and breast cancer risk was considered inconclusive, although there was substantial evidence from animal studies that numerous chemicals in tobacco smoke are mammary mutagens and carcinogens.

Some human data also showed that tobacco smoke carcinogens reach the breast and are metabolically activated, bind to DNA, and cause DNA damage. In 2009, the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk concluded that both active and passive smoke exposures increase breast cancer risk. The panel concluded that: "(1) the association between active smoking and breast cancer is consistent with causality;" and "(2) the association between secondhand smoke and breast cancer among younger, primarily premenopausal women who have never smoked is consistent with causality." Most recently, investigators from the Nurses' Health Study evaluated associations among 8,772 women with breast cancer in a cohort of 111,140 participants and concluded that "active smoking, especially before the first birth, may be associated with a modest increase in the risk of breast cancer."[205]

Lack of associations between breast cancer and smoking in some studies could be due to the potential anti-estrogenic effects of smoking, which could counter the adverse effects of chemical carcinogens in the breast.[206] For example, cigarette smoking induces CYP1A2, which decreases the level of circulating estradiol. Induction of other CYP enzymes in breast tissue by smoking also may affect levels of reactive metabolites, both estrogens and chemical carcinogens. The competing effects of smoking on estrogens and carcinogens could hinder the epidemiologic assessment of breast cancer risk because genetic differences in metabolism and detoxification may make some women more susceptible to the effects of tobacco smoke than others. Numerous investigations have been conducted on the potential modification of associations between smoking and breast cancer risk by genetic variants in carcinogen metabolism pathways. A meta- and pooled analysis with more than 5,000 cases and 5,000 controls showed that women with NAT2 genetic variants, resulting in slower detoxification of carcinogenic aromatic amines, were at an increased risk for breast cancer with smoking.[207] A pooled analysis of similar size, however, did not replicate an association between tobacco smoke, NAT2 gene variants, and breast cancer risk.[208] Despite these conflicting results in relation to genetic variability, the evidence reviewed by the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk and the recent results of the largest (to date) prospective study of smoking and breast cancer strongly suggest that smoking increases the risk of breast cancer.

The section above on Chemical Exposures (see Section 6.2.6) provides evidence that nonhormonal chemical carcinogens present in tobacco smoke, such as polycyclic aromatic hydrocarbons (PAHs), aromatic amines (AAs), and N-nitroso compounds, play a role in breast cancer. The section also noted that these chemicals may be stored in adipose (fat) tissue in the breast, and breast tissue can metabolically activate these carcinogens. An additional line of evidence supporting this hypothesis is that mutations in the Tp53 tumor suppressor gene are common in breast cancers; and Tp53 mutations are more prevalent in smokers, especially long-term smokers, than among nonsmokers.[209]

Gaps

Some of the numerous epidemiologic studies of the relationship between tobacco smoke exposure and breast cancer risk have evaluated the potential modifying effects of genetic factors. Nevertheless, evidence is inadequate to explain differences in breast cancer risk among women with similar tobacco exposure. More research also is needed to determine the association between smoking and the risk of breast cancer subtypes.

Recommendations

- Use existing breast cancer GWAS to stratify by smoking behaviors to identify specific genes that put some women who smoke at increased risk for breast cancer.

- Support studies that evaluate the relationship of tobacco exposure to breast cancer subtypes.

- Support research on the role of smoking in pregnancy on breast cancer risk in the offspring, as well as the effects of secondhand smoke exposure during childhood environment on risk.

6.3 Overarching Themes, Research Directions, and Recommendations

In this section, we summarize overarching, major areas for future breast cancer research and develop specific recommendations related to these important areas. Our goals were to review the research in the context of the animal-to-human paradigm, couple the research with an evaluation of life-stage susceptibility, and embrace the harmonization of data and time-sensitive biospecimen collection using the best methodology available. Ultimately, these recommendations will fill in knowledge gaps necessary to develop prevention strategies for implementation during potential windows of susceptibility for breast development and cancer initiation and promotion.

As evidenced by the limited research citations, the Committee calls for a greater effort to address breast cancer disparities among the underserved and minority populations that have a higher risk for mortality. The Committee also recognizes the need for novel/improved methods to measure environmental exposures. In addition, we recognize the complexity of breast cancer and underscore the need for research on intrinsic tumor subtypes and potential variations in the effects of exposures by subtype.

At the beginning of this section, we identify conceptual themes for accelerating progress in research on breast cancer and the environment (Section 6.3.1). The two themes focus on transdisciplinary research and a life-course approach to unraveling the role of environmental exposures at different periods of development and adulthood. After establishing these two thematic areas, we discuss areas where additional research is needed (Section 6.3.2) and propose specific recommendations to explore:

- Etiology/causes of breast cancer overall and by subtype,
- Etiology/causes of breast cancer by race and ethnicity,
- Testing of environmental exposures,
- Monitoring of environmental exposures,
- Methodological issues relevant to the study of breast cancer and the environment, and
- Risk assessment.

The discussion of each theme and research area is followed by specific recommendations that have policy implications. Policy affects how research is conducted, reported, interpreted, translated, and communicated. Examples of policies that can facilitate and encourage research on breast cancer and the environment include those that require data sharing for research purposes, collection of certain types of data, and standards for data collection. Policy, therefore, is the backbone for prioritizing research and surveillance. This chapter ends with a table of key research needs organized under four critical questions (i.e., which exposures, what effects, what underlying mechanisms, and who is at risk). Table 6.3 indicates whether the research needs should be addressed in human or animal studies or both.

> Policy affects how research is conducted and reported. Policy also affects how research results are interpreted (e.g., weight-of-evidence criteria) which, in turn, affects the decision to conduct further research on a topic. Finally, policy affects how results are disseminated and translated into effective preventive strategies and treatments, especially when action by government and industry is required.

6.3.1 Overarching Themes

Throughout this report, the Committee emphasizes the importance of transdisciplinary research and a life-course approach to the study of breast cancer and the environment. These approaches are likely to accelerate progress in our understanding of breast cancer etiology and methods to prevent this disease.

Theme A: Transdisciplinary Research

This and the previous chapter provided ample evidence of the complexities involved in understanding the role of environmental factors on breast cancer risk and the value of using research from animal models and human studies, considering basic underlying mechanisms of carcinogenesis and understanding

human behavior and societal context. Although the chapters showed substantial scientific progress in our understanding of breast cancer as well as limited knowledge about the role of the environment, most of the research in this area was conducted by individuals or teams of scientists from the same disciplines. Yet, evidence suggests that team science and the use of transdisciplinary approaches to conduct the research can achieve more success and may accelerate the research process.[210, 211] The transdisciplinary approach involves researchers working jointly using a shared conceptual framework and drawing together discipline-specific theories, concepts, and approaches to address a common problem.[212]

Transdisciplinary collaboration also should create an infrastructure of scientists, clinicians, and breast cancer advocates who work together to examine the role of clinical, physical, biological, and social factors—individually and in interaction with genetic factors—on breast cancer initiation and progression. The involvement of researchers from multiple disciplines facilitates an understanding of how various environmental exposures and susceptibility factors interact at different points in mammary gland development to influence breast cancer risk. The involvement of a wide range of stakeholders, including clinicians and advocates, throughout the research process helps to ensure timely translation of findings into useful public health information. Improvements in the consistency of protocols and collaborative efforts among researchers and clinicians are paramount to improving breast cancer research and data analysis so that policymakers can provide recommendations and initiate policy changes that are relevant to human health. Examples of transdisciplinary breast cancer research programs can be found in Chapter 7.

Recommendations

- Support transdisciplinary research in breast development and breast cancer risk, recurrence, and survival by developing research initiatives that require a collaborative approach, team science, and communication experts to link results to policy arenas at the federal, state, and local levels.
- Support scientific exchanges between epidemiologists and animal scientists to encourage and facilitate transdisciplinary research. This will enable more life course approach studies in rodent models to be guided by preliminary data or hypotheses generated within human studies. Alternatively, more prospective longitudinal epidemiologic research should be guided by the results of animal experimental research.
- Convene epidemiologists, clinicians, genomics specialists, and other specialists to plan and conduct transdisciplinary studies in women with common environmental risk factors and/or specific breast cancer subtypes. These types of studies are needed to identify the molecular mechanisms that underlie the risks.
- Implement data-sharing policies that make data widely available to investigators outside of the original team and facilitate new data uses and innovative hypotheses and approaches beyond the aims of the original research. Biospecimens should be made available for new research activities (within the scope of the original informed consent) after the original aims of research are completed. Current National Institutes of Health (NIH) data-sharing policies, including policies for data posting and sharing, can be seen at http://grants.nih.gov/grants/policy/data_sharing/ and http://gwas.nih.gov/pdf/Data%20Sharing%20Policy%20Modifications.pdf.[213, 214]
- Fund projects aimed at developing or improving databases that link human and rodent data in breast development and cancer. These databases should include information on carcinogens, biospecimen availability, biomarkers, and research results.
- Develop training programs in transdisciplinary research for clinicians, advocates, epidemiologists, environmental scientists, and biologists, and encourage training in the language and content of multiple disciplines. Also, develop training in effective media communication for scientists.

Theme B: Life Course Approach

The life course approach to breast cancer was initially hypothesized by Tricopolou, who stated that hormonal exposures *in utero*, and therefore before the age at menarche, could increase breast cancer risk[38, 215] For example, girls born of high birth weight, a marker for hormonal exposures, are at increased risk for breast cancer.[38] In addition, women exposed to DES *in utero* are at risk for breast cancer. One of the lessons learned from the article by Cohn and colleagues on DDT exposure at specific ages and breast cancer risk is the importance of the timing of the environmental exposure (i.e., those under 14 years of age were at higher risk than those who were more than 14 years old[216]). Likewise, the age at radiation exposure in Hiroshima determined whether a girl was at risk for breast cancer.[217] Both of these studies and others identify the importance of the timing of exposure during puberty and subsequent risk.[55] Future research, therefore, should focus on the role of environmental exposures and breast cancer risk across the life course.

Recommendations

- Ensure adequate and sustained funding of new and ongoing prospective longitudinal human studies that collect early life exposure and reproductive developmental data, which can shed light on breast density, benign breast disease, and breast cancer risk over a lifetime (e.g., the Center for the Assessment of Mothers and Children [CHAMACOS] in the Agricultural Health Study, BCERP, National Children's Study, and others).

- All industry, government, and academic laboratories that perform chemical testing should include exposure assessment *in utero* and in infancy (e.g., measurements of blood or urine levels) when conducting their exposure studies. Mammary gland or cell evaluations also are needed to collect as much information as possible on exposures.

6.3.2 Research Directions

In reviewing the evidence discussed in this chapter as well as in Chapter 5, the Committee identified several areas of research that must be expanded to advance our understanding of breast cancer and the environment. These research areas or "directions" are described in this section.

Etiology of Breast Cancer and Breast Cancer Molecular Subtypes

Nearly every section of this chapter noted the absence of information on the various subtypes of breast cancer beyond estrogen- and progesterone-receptor positivity. Even this information is not available from many studies. Very little is known about the basis for the sociodemographic, ethnic, psychological, and biologic determinants of tumor subtypes. The impact of endogenous factors or exogenous environmental factors (e.g., lifestyle, chemicals, endocrine modulators) as potential determinants or modifiers of breast cancer subtypes is not known. These data are essential for both risk prediction and therapeutics.

Recommendations

- Investigate the associations between environmental exposures and risk of specific breast cancer subtypes, including identifying susceptible mammary cell type(s), mechanisms of initiation, and the life stages when women and men are more susceptible to different subtypes.

- Investigate the role of early life diet and other lifestyle behaviors, possible chemical exposures, and social factors—in addition to biologic data—to understand the etiology of disease and to develop primary prevention strategies in breast cancer.

- Support research to discover new mechanisms of cancer initiation, progression, and treatment, including the role of stem cells, cellular reprogramming, breast density and breast density changes, and nonmutagenic mechanisms in breast cancer risk and progression.

- Support large epidemiologic cohort studies of environmental factors and the risk of breast cancer and its recurrence, mortality, and second primaries. These studies should include biospecimen

- collection (e.g., tumor tissue, blood, and so forth) and biobanking, cancer treatment data (for breast cancer survivor cohorts), and detailed examination of breast cancer subtypes.

- Support studies in both mouse and rat models to identify the cell type of origin of different cancer subtypes, the life stage of initiation, the nature and mechanisms of the initiating agents, and how endogenous factors and exogenous environmental factors impact these events.

Research on the Environment and Breast Cancer Subtype Among Ethnic Groups and Underserved Populations

Breast cancer research has focused primarily on non-Hispanic White women. Insufficient evidence exists on the role of environmental exposures in breast cancer risk in medically underserved populations, including Hispanic and African American women as well as certain racial/ethnic subgroups. Often, breast cancer studies include few individuals from racial and ethnic minority groups. Researchers also may not examine the subgroups separately and, therefore, cannot determine whether risks vary by race and ethnicity. Currently, only a few studies relevant to breast cancer and the environment focus on these groups (e.g., *The Black Women's Health Study*) or include large numbers of women from these groups (e.g., the *California Teachers Study*). More data are needed to examine breast cancer subtypes and other prognostic indicators in racial/ethnic minorities and other population subgroups. These data are essential for developing primary prevention strategies to reduce disparities in breast cancer outcomes.

As noted in section 6.2.5, women of color and low-income women often have a disproportionate burden of exposure to environmental contaminants in the air, water, and soil in their communities. Racial/ethnic minority groups also tend to have increased levels of psychosocial stress due to neighborhood and family-based factors,[218-221] The combination of high exposure to environmental contaminants, combined with high levels of stress and various lifestyle factors, may lead to patterns of breast cancer that differ from those found in the general population. Environmental justice studies have documented neighborhood-based features and found high levels of pollutants in the environments in which women live and work.[222, 223] With the exception of the Sister Study, however, these studies tend to lack comprehensive data collection on physical and chemical exposures to complement the reproductive, lifestyle, and other data collected. Accelerating research on breast cancer and the environment will require increased numbers of study participants from underrepresented populations, improved collection of data on breast cancer subtypes and physical and chemical exposures in these populations, and increased numbers of researchers with the skill sets needed to conduct research in underrepresented communities.

There is a great need for increased support for studies of breast cancer and possible causative risk factors in Hispanic, Asian American, African American, and Native American women.

Recommendations

- Develop research initiatives to gather data on population subgroups by breast cancer subtype. For example, data are needed on the role of stress, socioeconomic factors, lifestyle characteristics, neighborhood and other environmental factors—including the physical and chemical environment and the role of the built environment (i.e., the human-made environment, including buildings, spaces, and roads that influence health behaviors such as physical activity).

- Develop research initiatives to obtain data on population subgroups by prognostic indicators of breast cancer subtypes. Data from this research would be invaluable to understanding and developing interventions to reduce disparities in breast cancer mortality. Support targeted research to better understand the specific environmental risks for breast cancer in underserved populations as well as targeted policies to ameliorate environmental disparities (See the discussion of biomonitoring ethics in Chapter 8).

- Examine population subgroups that exhibit high rates of certain breast cancer subtypes to elucidate mechanisms by which specific risk factors lead to these subtypes. For example, African American and Latina women are more likely to have children at a younger age, have more children, and not breast feed.[224] These reproductive factors have been linked to ER– or basal-like breast cancer subtypes, which also are more prevalent among African American women.[225]

Monitoring Exposures

The recent Institute of Medicine (IOM) report on breast cancer and the environment called for better science to monitor exposures and to understand the "exposome,"[226] which represents "the totality of exposures received by a person during life, encompasses all sources of toxicants and, therefore, offers scientists an agnostic approach for investigating the environmental causes of chronic diseases."[227] Biologic and environmental monitoring provide valuable data that can be used to prioritize chemicals for further testing, environmental mitigation, public health interventions, and regulations.

Policies can support biomonitoring of exposures, which is the process of measuring the presence of environmental exposures in blood, tissue, urine, saliva, breast milk, cord blood, and other biospecimens. National biomonitoring programs include the CDC's NHANES[228] and the now inactive National Human Adipose Tissue Survey. Other programs that provide environmental exposure monitoring include the National Institute of Environmental Health Sciences (NIEHS)-EPA Centers for Children's Environmental Health and Disease Prevention Research and the NIEHS Superfund Basic Research Program. Policies also need to support the tracking of exposures through environmental monitoring, which measures exposures in the ambient air, water, ground, fish and wildlife, and other parts of ecosystems.[229] Major environmental monitoring programs include the National Atmospheric Deposition Program/National Trends Network; EPA's Air Toxics Program, Environmental Monitoring and Assessment Program, Safe Drinking Water Information System, and Toxic Release Inventory; the U.S. Geological Survey's National Water Quality Assessment Program; and many others. Examples of the potential impact of biologic and environmental monitoring interventions on exposures to both known and biologically plausible health hazards include:

- The ongoing program of monitoring efforts, research, and interventions to reduce lead levels in children's blood in the United States, which is a notable success story.[230]

- A dietary study of BPA that demonstrated that eating a diet free of packaging containing BPA contaminants led to an average 66 percent decrease in urinary BPA levels after only 3 days.[57] Consumer demand for BPA-free cans is increasing and, as part of a lawsuit settlement, the FDA considered whether to ban BPA in 2012.[231] The FDA ultimately decided not to ban BPA but to continue the study of this chemical.[232]

- A series of articles by the Silent Spring Institute revealed widespread exposures to endocrine disruptors, including flame retardant polybrominated diphenyl ethers (PBDEs) in household dust.[233] The articles reported the results of a study that found that, in geographic areas where PBDEs were present in higher levels in household dust, increased levels of PBDEs also were present in people's bodies based on serum samples collected through NHANES.[234] The articles recommended household exposure studies to inform state and federal management policies regarding the use of hormone-disrupting chemicals in household products.[235]

Although many monitoring programs exist, strategic expansion is needed to improve the ascertainment of exposures across the life course and provide representation of all population subgroups, including underserved and under-researched groups[236] as well as "fenceline" communities that are in close proximity to industry or waste sites. The monitoring programs should include coverage of high- production volume chemicals; persistent, bioaccumulative and toxic chemicals; and other exposures related to

emerging technologies. Data collection across federal agencies should be coordinated.

Given that the effects of radiation exposure accumulate over the lifetime, policies also are needed to support the monitoring of an individual's exposure to radiation.[226] Computerized medical records and other modes of tracking exposures to medical radiation (CT scans, fluoroscopy, mammography, interventional radiology, and radiotherapies) are needed across populations. Medical devices that emit radiation should be monitored to ensure that machines are calibrated to radiation doses that provide optimal imaging at minimal exposures. These calibrations should take into consideration age, body mass, and other individual characteristics that could lead to overexposure to radiation.

Lifestyle, social context, economic determinants, and disproportionate environmental exposures are likely to create disproportionate risks among minority and poor populations. As a result, there is a need for targeted research to better understand the specific environmental risks for breast cancer in these populations as well as targeted policies to ameliorate environmental disparities.

Recommendations

- Expand biomonitoring programs and increase coordination across federal, state, local, and tribal biomonitoring programs. The National Conversation on Public Health and Chemical Exposures articulated several priorities to enhance biomonitoring,[237] as did the earlier report on breast cancer and the environment to the CDC on the International Summit on Breast Cancer and the Environment.[238] Developing methods to measure those high-priority chemicals can address biomonitoring gaps. Biomonitoring programs should standardize data collection and analysis to better support the use of these data in research and risk assessment as well as in setting priorities for reducing environmental exposures. Biomonitoring should include chemicals in food, household, cosmetic, and other common consumer products as well as pharmaceuticals. Biomonitoring efforts also should focus on radiation exposure.

- Devote adequate resources to communicating biomonitoring results to research participants, the public, and policymakers.

- Expand biologic, environmental, and lifestyle factor monitoring to improve ascertainment of exposures across the life course and representation of underserved and under-researched populations to accelerate research on breast cancer and the environment.

- Implement necessary policy changes so that national sampling data are more readily available to regulatory agencies and researchers, in particular, to allow analysis by geographic location, occupation, and other characteristics.

- Support research focused on resolving methodologic challenges in biomonitoring related to hormones and environmental contaminants. Develop standardized biospecimen collection and valid approaches to occupational exposure monitoring. High-quality biomonitoring will provide accurate data for exposure assessments among various age groups, including children and infants.

Testing Environmental Exposures

Many regulatory agencies' authorizations lack toxicity data requirements prior to the release of chemicals into the environment, although many require risk assessment after their release.[239] For instance, when the Toxic Substances Control Act (TSCA) was implemented in 1976, more than 62,000 chemicals were grandfathered in without testing requirements, which allowed their continued commercial use.[d] Approximately 200 of these chemicals have been tested since TSCA was enacted.[240] In addition, 85 percent of new chemicals reported under the TSCA lack data on chemical health effects.[241] As a result of the lack of policy mandates and capacity to fully

[d] http://www.epa.gov/opptintr/existingchemicals/pubs/tscainventory/basic.html#background.

test chemicals as they come to market, complete toxicological screening data are available for only 7 percent of the more than 84,000 chemicals currently registered for use.[188]

Improving the TSCA is a priority for collecting the data needed to generate and test hypotheses regarding the effects of a wider range of chemicals on breast cancer risk and, ultimately, for preventing environmentally caused disease.[237, 242] Indeed, the EPA itself has called for stronger policies for chemical testing.[188] In addition, multiple federal agencies are involved in the testing, monitoring, and regulation of chemicals, including several EPA and FDA offices, the Consumer Products Safety Commission, the CDC, and the NIEHS. However, of these, only the NTP, within the NIEHS, consistently evaluates mammary tissue for the effects of chemicals that are tested. The EPA does not require mammary evaluation as part of its pubertal protocol, and other agencies are considering moving away from intact animal studies to cell models that do not include normal mammary cultures.

Testing is complicated by the classification systems used to identify carcinogens. These systems have various criteria for study inclusion, and the lack of standardized criteria for mammary carcinogen assessment[243] complicates comparisons across studies. This likely is part of the reason that much of the existing toxicologic data related to mammary gland tumors have not been used in chemical risk assessment or regulation.[187] Interestingly, three of the five chemicals suggested as contaminants of the Camp Lejeune Marine base water supply in the 1950s to 1980s (benzene, vinyl chloride, and 1,2-dichloroethane[244])—and theorized to cause a spike in male breast cancer incidence—are on the list of 216 chemicals that affect the breast following adult exposures.

Chemicals identified as biologically plausible risks for breast cancer and chemicals with similar molecular structures need to be included among prioritized chemicals for testing. Testing frequently does not consider issues of particular relevance to breast cancer, such as cellular and molecular pathways, altered mammary gland development, the breast microenvironment, epigenetics, and susceptibility (e.g., early puberty).[226, 246] A need also exists for rapid validation and implementation of emerging testing modalities.

As David Christiani, M.D., of the Harvard School of Public Health noted, policies that "require premarket safety testing, reduce industry influence on regulations, and control the importation of toxic chemicals and products," are necessary to prevent cancer. "This approach should be the cornerstone of a new national cancer prevention strategy emphasizing primary prevention."[245]

Many chemicals and pharmaceuticals are EDCs that have been inadequately tested for their ability to contribute to breast cancer[247] and may have long-term health implications for those exposed, as in the case of DES.[47, 226] A number of EDCs are used in readily available consumer products, including personal care products, household cleaning products, and food contact substances, and have been found to affect indoor air quality.[166, 226] The majority of chemicals that are used in food, household, cosmetic, and other products in the United States have not been tested for health effects, and fewer have been tested for potential breast cancer risk.

Recommendations

- Prioritize chemicals that are produced in high volumes for which there is biologically plausible evidence of their role in the development of breast cancer. Consider factors that are particularly relevant to breast cancer, such as cellular and molecular pathways, altered mammary gland development, the breast microenvironment, epigenetics, and susceptibility (e.g., early puberty).[226, 246] Require that mammary gland tissue be analyzed in rodent models when testing chemicals, pharmaceuticals, and food additives in industry and government health evaluations. To test compounds adequately that are in commerce currently requires changes in the approaches to

- and scope of testing. Consideration should be given to detecting possible low-dose effects and multiple chemical mixtures when common pathways are known.

- Improve the oversight of cosmetics and personal care products as well as household cleaning and food containment products. The recent IOM report highlighted the need for the FDA to provide better oversight of cosmetics and personal care products.[226] Testing of the products should include an evaluation of the effects on mammary tissue or cells.

- Support research to develop: (1) testing methods that identify mammary gland effects (e.g., cell-based systems that mirror the complex cellular makeup of the breast); and (2) identification of biomarkers in animals that can be used in assessing human breast cancer risk. Chemical testing research should transition from testing one chemical at a time in hundreds of rodents to more high-throughput, yet biologically relevant, methods that assess endocrine-disrupting effects alongside other mechanisms. Biomarker identification is needed, which would enhance our ability to predict those with greatest susceptibility to breast tumors.

Methodological Issues in the Assessment of the Environment and Breast Cancer

Our review identified a few areas in which methodologic research is needed to accelerate the understanding of the role of environmental factors in the development of breast cancer. These research areas relate to the kinetics of exposure and statistical methods for analyzing multiple factors and pathways that lead to the development of breast cancer.

Kinetics of Exposure

Kinetics is the study of the rates of chemical processes—including the speed of reactions to chemicals, such as those in the soil and water—as well as the differences in reactions among different individuals to the same environmental exposure. Data are limited on the kinetics of exposures to chemicals and other physical elements. Moreover, few investigations examine the pattern of the reaction time to various dosages of an exposure.

Recommendations for Studying the Kinetics of Exposure

- Conduct research on the kinetics of exposure in humans and animals in addition to research on the mechanisms that underlie exposure, especially with regard to windows of susceptibility.

- Evaluate minimal levels of exposure.

- Explore nonlinear and nonmonotonic exposures-disease relations.[204]

Statistical Methods Development

New statistical models are needed to fully evaluate the role of multiple chemical exposures that may influence known breast cancer risk factors, such as the age of puberty onset, body size, fertility, and reproductive outcomes. For example, if an exposure leads to an earlier age at menarche, which in turn leads to enhanced breast cancer susceptibility, simply adjusting for age at menarche in a statistical analysis may be inappropriate.

Recommendations for Statistical Methods Development

- Develop new statistical tools (e.g., Bayesian models or propensity scores) that can account for multiple factors and pathways, complex interactions, and nonlinear dose relationships leading to the development of breast cancer.

- Assess whether specific environmental exposures enhance traditional breast cancer risk prediction models, such as those developed by Gail and colleagues.[248]

Risk Assessment

Environmental health protection is based primarily on three components: hazard identification, risk assessment (which includes exposure assessment), and regulation. Hazard identification is the process

by which entities formally recognize compounds as toxic. Chemicals can be considered toxic if they are carcinogens, neurotoxins, reproductive toxins, EDCs, or if they otherwise disrupt healthy physiological function. Scientists and public health organizations, for example, increasingly are calling for the evaluation of the health hazards of EDCs.[247, 249-251] Risk assessment is the current process for organizing and analyzing data to define the potential health effects that may result from exposure of individuals or populations to hazardous materials and other environmental agents, such as radiation. Risk assessments are used in regulatory decision making. The process of identifying, assessing, and regulating carcinogens can be illustrated as follows: groups such as the IARC or the NTP in its Report on Carcinogens[89] classify agents as carcinogens when animal or human evidence accumulates to a convincing level as determined by panels of experts. After identification as a "possible, probable, or known" carcinogen, agencies such as EPA assess the levels and routes of exposure of concern and quantify the level of risk to humans from the known or suspected carcinogens. Finally, if the assessment indicates risk above levels of concern, regulation of the agent is promulgated to mandate reduction or elimination of the hazardous exposure.

Emphasize hazard-based decision making to support targeted public health interventions.

Recommendations

The current approaches to hazard identification, risk assessment, and regulatory action have significant weaknesses. We recommend the following approaches to ameliorating these weaknesses:

- Develop new methods to facilitate high-throughput testing and consider possible unanticipated effects from individual and combinations of exposures.[252, 253] The NTP has proposed revising its testing program to include less expensive, higher throughput, alternative assays for screening a large number of substances and establishing priorities for additional, more extensive agent-specific mechanistic studies. In December 2011, the NIEHS, National Human Genome Research Institute, EPA, and FDA began collaborating on a program to test a 10,000-compound library for potential toxicity using a high-speed robotic screening system.[254] Even with high-throughput methods and intelligent prioritization of chemicals, however, the limitations of testing programs, particularly when combined with the time involved in implementing regulations, argue for a precautionary approach to regulation.

- Implement risk assessment approaches across agencies to address factors such as cumulative and aggregate exposures to chemicals that may act additively[255, 256] or synergistically,[257, 258] windows of susceptibility, nonlinear dose-response relationships, epigenetics, and the complexities of epidemiologic data.[247, 259-264]

- Consider the range of susceptibilities across the population when conducting risk assessments; when data are unavailable, limited, or insufficient, use assumptions and default safety factors that will protect the most susceptible individuals, including populations that are under-researched. Emphasize decision making based on life stage and dose response[259] to support targeted public health interventions and facilitate the development of recommendations and regulations as needed. To protect public health, guidance is needed on how to act in the face of uncertainty or incomplete knowledge. This guidance should rely on the weight of the best available evidence in decision making.[262] For instance, the French National Academy of Medicine[251] highlighted concerns about the EDC known as BPA. Although the Academy did not feel that sufficient alternatives to BPA existed for food contact items to call for a ban, it did recommend preventive measures for persons at high risk of endocrine disruption, including young children, people with hormone-dependent cancer, and pregnant and lactating women[251] More evidence is needed to guide decision making that takes into account interspecies differences, dose-response relationships, aggregate exposures, duration of exposure, acute versus chronic conditions, and other unknowns.[265] In addition, other characteristics, such as age,

- life stage (e.g., infancy, puberty, menopause), medical conditions (including pregnancy) and treatments, genetically determined differences in metabolism and repair, as well as other cancer risk determinants, must be accounted for in current risk assessment techniques. Finally, a commitment to a hazard-based approach for regulating chemicals is necessary to protect public health.

- Integrate information from a variety of sources, such as permit and mineral lease records, agricultural application and run-off data, and material safety data sheets, into datasets for use in research on breast cancer and the environment and for public information. Federal agencies, including the FDA, Consumer Product Safety Commission (CPSC), U.S. Department of Agriculture (USDA), Occupational Safety and Health Administration (OSHA), and a number of EPA offices, independently engage in efforts to characterize hazards, exposures, and risks of chemicals and radiation from a range of sources that includes air, water, agricultural, industrial, and consumer products.

6.4 Overview of Key Human and Animal Research Needs

We have defined the priority areas for the next generation of breast cancer and the environment research.

In this chapter, we used an evidence-based systems approach to evaluate the state of the science and identify gaps in the field with the aim of prioritizing emerging scientific opportunities to answer the question, "What should the next generation of research on breast cancer and the environment look like?" We employed the animal-to-human paradigm based on the principle that examining and integrating both animal and human research findings will accelerate translation of research into clinical practice and environmental policy.

Table 6.3. Overview of key human and animal research needs

Note: Priority research needs in rodents and humans are delineated under four critical questions, followed by the goals that each question addresses.

1. Which environmental exposures impact breast cancer risk or the susceptibility to breast cancer?

- **Identify environmental and lifestyle factors (and the combinations thereof) that impact the breast.**
- **Develop technologies and methodologies for exposure assessment that are relevant at specific life stages or across the life course or generations.**
- **Develop a methodology for assessing exposures.**

Research Needs:	Human	Rodent
Expand testing of environmental exposures alone and in combination (chemicals and other environmental exposures) for specific effects on breast/mammary gland development, function, and susceptibility to breast cancer.	✓	✓
Develop low-cost, feasible, low-response burden- and age-appropriate technologies to assess exposures in humans.	✓	
Develop improved analytical methods for precise and reliable chemical measures in biologic matrices. Validate novel and existing analytical methods.	✓	✓
Develop tracking systems as well as monitoring and surveillance programs to improve the understanding of individual exposures.	✓	When applicable
Measure internal exposure levels in biospecimens (e.g., blood, urine, fat) and how they change with the pharmacokinetics of exposures.	✓	✓
Validate the population-based tracking systems for modeling human exposures.	✓	
Identify biomarkers of exposure relevant to breast cancer susceptibility.	✓	✓

Table 6.3. (continued)

2. When do the exposures have their (greatest) effects?		
• Identify the windows of susceptibility for environmental exposures for breast cancer risk and recurrence.		
Research Needs:	**Human**	**Rodent**
Identify exposure-related risk based on life stage in relation to breast development (e.g., *in utero*, postnatal, puberty, adulthood, pregnancy, menopause).	✓	✓
Identify exposure-related risk by gender.	✓	✓
Identify the impact of environmental exposures in breast cancer survivors on recurrence, progression, and metastasis.	✓	✓
Utilize current biobanks, clinical networks, and cohorts to expand the inquiry into environmental estrogens and breast cancer across the life span.	✓	✓
3. What are the underlying mechanisms for the effect of environmental exposures on breast cancer risk or recurrence?		
• Identify mechanisms that underlie exposure-related risk. • Develop preventative and therapeutic modalities based on the identified mechanisms.		
Research Needs:	**Human**	**Rodent**
Identify the relevant animal, tissue culture, and high-throughput screening models to test the impact of environmental exposures on susceptibility to breast cancer across the life span and genders (e.g., knock-out or -in models, pathway analyses, and so forth).	✓	✓
Define how exposure-induced mechanisms cause altered breast development, function, and susceptibility to breast cancer in both females and males (direct or indirect via endocrine disruption—brain, gonads, fat, and so forth).	✓	✓
Develop improved statistical approaches for modeling the effects of multiple exposures.	✓	✓
Determine how and when environmental exposures may impact breast cancer subtypes and appropriate subsequent therapy (i.e., BPA and tamoxifen antagonism).	✓	✓
Develop prevention and intervention approaches.	✓	✓
4. Who is at risk for breast cancer from environmental exposures?		
• Identify those at high risk for breast cancer to inform preventive intervention strategies.		
Research Needs:	**Human**	**Rodent**
Identify the effects and mechanisms of exposures in individuals at high risk due to genotype (i.e., genetic susceptibility with known mutations or common genetic variants that modify the effects of exposure).	✓	✓
Develop biomarkers and utilize sophisticated prediction models to identify high-risk individuals who are impacted by exposures.	✓	✓
Identify the effects and mechanisms of exposure interactions with phenotype and known breast cancer risk factors (e.g., breast density, obesity, life style, and tumor subtype).	✓	✓
Investigate the unique issues, concerns, and related research needs for minority and other special populations (e.g., people in specific occupations or residing in fenceline communities) as they relate to breast cancer and the environment.	✓	

6.5 Conclusion

Despite decades of research focused on identifying the causes of breast cancer, many risk factors remain to be identified. Furthermore, research on the potential associations between environmental factors and breast cancer risk has yielded little conclusive evidence. Although this lack of progress has been frustrating, researchers have identified multiple factors that could account for the inability to elucidate the causes of breast cancer. First, the majority of epidemiologic studies have examined the effects of environmental factors on breast cancer at the time of diagnosis. As discussed in Chapter 5, substantial evidence from animal studies and emerging evidence from human studies suggest that the timing of exposures during the life course is a critical determinant of the impact on breast cancer risk. Future studies must consider the timing of exposure and window of susceptibility to pertinent cellular and molecular effects to elucidate the environmental causes of breast cancer. Second, as discussed in Chapter 3, breast cancer is not one disease, and causal pathways are likely to vary for molecular subtypes (e.g., Luminal A versus basal-like breast cancer). Examination of associations by breast cancer subtype may greatly advance knowledge in this area. Heterogeneity in susceptibility further complicates our understanding of the role of environmental factors in breast cancer etiology. Susceptibility to specific environmental factors may be influenced by age, reproductive characteristics, or any of a wide range of other personal characteristics or exposures. Differences in susceptibility to environmental exposures may be due to common variations in the genes that encode enzymes, which affects metabolism, DNA repair, and other pathways related to carcinogenesis. Finally, exposures to environmental toxicants, such as herbicides, pesticides, and those in household products, are extremely difficult to monitor and quantify. All of these challenges must be addressed in future studies.

Humans are exposed to a wide range of environmental factors (from chemicals and lifestyle) in various combinations and mixtures. For the most part, animal toxicologic testing of environmental chemicals has failed to examine comprehensively the effects of a wide range of relevant exposures on the mammary gland and adopt dosing regimens that fully characterize the effects of timing. Innovative research using a diversity of animal models that mimic the genetic background of the human population and incorporating new, computational methods to guide the search for gene and environmental interactions is critically important to understanding normal mammary development patterns and how they change in response to stressors. Studies of the relevant mixtures to which human populations are exposed provide an opportunity for discovery and hypothesis generation. Integration of disciplines across the animal-to-human paradigm offers the opportunity to garner the fullest understanding of the contribution of environmental factors to breast cancer risk, underlying mechanisms, and the potential for prevention strategies. Animal and human research each have their unique advantages and limitations, indicating that scientists can learn best from the use of both research modalities.

The research recommendations presented in this chapter are directed at accelerating progress toward reducing the high cost of breast cancer—both human and economic. Adoption and promotion of policies that provide guidance, resources and, where appropriate, mandates, may be necessary to ensure rapid and effective implementation of a research agenda that prioritizes breast cancer prevention. Policies in support of this critical research area would strengthen chemical testing and exposure monitoring as well as establish standardized methods for biomonitoring across the life course and among underserved and under-researched populations. Policies also are needed that support transdisciplinary risk and hazard assessment models, which consider windows of susceptibility across the life span; low dose, aggregate, and cumulative exposures and their effects on mammary gland development; and interactions between environmental and genetic risks factors for breast cancer.

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7
CHAPTER

Research Process

7.1 Introduction

The Breast Cancer and Environmental Research Act of 2008 charged the Committee with examining current research on breast cancer and the environment and to recommend changes that improve the associated research portfolio. The Committee analyzed federal and nonfederal research investments and initiatives in breast cancer to characterize the extent to which these activities support research on the role of environmental factors in breast cancer. The results are presented in this chapter and include: (1) a discussion of relevant funding mechanisms, initiatives, and programs in place today; (2) an estimate of the fraction of federally funded breast cancer research specifically focused on environmental factors related to breast cancer prevention and disease etiology; and (3) a discussion of the roles and an analysis of the contributions of nonfederal organizations in funding research on breast cancer and the environment.

The chapter also discusses important aspects of the breast cancer and the environment research enterprise, such as ways that scientific innovation is being promoted and the involvement of advocates and other stakeholders in research efforts. The chapter concludes with a discussion of gaps related to research funding and funding mechanisms and offers related recommendations to improve existing programs and processes relevant to breast cancer research.

7.2 Analysis of Federal and Nonfederal Research Investments in Breast Cancer

The Committee conducted a portfolio analysis of the federal government's mix of funded breast cancer research to understand research investment goals, investment gaps, and areas where different programs might be targeting similar goals. A portfolio analysis is an assessment of the elements of an organization's investments as a means of determining optimal future allocation of its resources. The size and complexity of the portfolio precluded the Committee from examining and classifying the tens of thousands of funded projects individually. Instead, we employed the classification coding system currently in use for all federal breast cancer funding by the National Institutes of Health (NIH) and the U.S. Department of Defense (DoD) for our analysis. We did not conduct a formal portfolio analysis of other

The Common Scientific Outline, a system for coding projects, classifies breast cancer research into seven categories: (1) biology; (2) etiology/causes; (3) prevention; (4) detection/diagnosis/prognosis; (5) treatment; (6) cancer control/survivorship/outcomes; and (7) scientific model systems.

federal agency funding because other agencies did not have coding and reporting systems that could identify research support relevant to breast cancer and the environment.

To examine NIH funding, the Committee used NIH's Research Portfolio Online Reporting Tools (the RePORT) system. RePORT currently classifies NIH funding into the following categories: (1) intramural research, (2) research centers, (3) research projects, (4) small business innovation research (SBIR) and small business technology transfer research (STTR), (5) training (institutional and individual), (6) research and development (R&D) contracts, (7) interagency agreements, and (8) other research (research grants not classified as research projects or research centers). In addition, the National Cancer Institute (NCI), DoD, and most nongovernmental organizations (NGOs) that fund cancer research rely on a project coding system developed by the International Cancer Research Partnership (ICRP) called the Common Scientific Outline (CSO). The CSO classifies cancer research into seven broad areas: (1) biology (normal functioning); (2) etiology or causes of cancer; (3) prevention; (4) early detection, diagnosis, and prognosis; (5) treatment; (6) cancer control, survivorship, and outcomes research; and (7) scientific model systems. Each of these seven categories is further divided into subcategories that facilitate more detailed classification.

The breast cancer and the environment research portfolio can be grouped into three broad categories. The first category includes basic, clinical, and population science studies and comprises most of the research funded by the NIH, the DoD, some NGOs, and at least one state-funded organization. This research principally focuses on discovering how environmental factors influence biological mechanisms involved in normal breast development as well as cancer and identifying lifestyle, chemical, physical, and genetic factors that, alone and in combination, influence an individual's risk of getting breast cancer. The first category also includes studies focused on preventing breast cancer by reducing or modifying risk factors. The second category of research focuses on public health and community-based prevention and detection of breast cancer. This research is funded primarily by the Centers for Disease Control and Prevention (CDC), some NIH Institutes (NCI and the National Institute of Environmental Health Sciences [NIEHS]), NGOs, and at least one state-funded organization. The third area of research informs regulation of environmental exposures and effective risk assessment relevant to breast cancer. Some U.S. Environmental Protection Agency (EPA) and U.S. Food and Drug Administration (FDA) research falls into this third category. All of these federal and nongovernmental agencies fund professional training and development programs, some of which are relevant to research on breast cancer and the environment. The Committee queried other federal agencies, such as the U.S. Department of Energy, which indicated that they did not conduct or support research on breast cancer and the environment for the fiscal years examined.

The federal breast cancer research portfolio is a blend of research that is prioritized and implemented by agencies through their internal research programs or targeted grant programs as well as investigator-initiated research that is applicable to breast cancer. Targeted programs define the knowledge gaps of interest and, based on an agency analysis and priority list, request researchers to suggest strategies for filling those gaps. Investigator-initiated research programs allow researchers the opportunity to identify knowledge gaps and justify why they are worthy of funding. Most agencies utilize both kinds of funding mechanisms. In addition, many agencies maintain and fund their own internal research programs.

Typically, agency and Institute and Center (IC) leaders evaluate their current research portfolios with respect to the agency or IC mission statement; opportunities and gaps as determined by agency/IC staff; input from the broad scientific, clinical, and public health communities a public and Congress, and their budget allocations. This information guides agency/IC leaders in making decisions about portfolio

balances across etiology, prevention, diagnosis, and treatment research areas as well as opportunities and gaps to pursue.

The peer review process plays a major role in determining the federal breast cancer research portfolio. All agencies use some form of peer review to identify research proposals with the highest scientific merit. Peer review involves the evaluation of research or other work by a group of experts in a relevant field. Internal (intramural) research programs typically are reviewed every 3 to 5 years by teams of outside scientists who report directly to agency administrators. Targeted and investigator-driven research programs typically are assessed by a two-tiered review process, such as the one recommended for the DoD by the Institute of Medicine (IOM) for DoD's Peer Reviewed Medical Research Programs.[1] In a two-tiered process, the first tier involves the proposed research being reviewed by a scientific review panel. This panel is made up of scientists with experience in and knowledge about the topics of the proposed research and, in a growing number of instances, advocates or other community representatives who can assess the potential impact and relevance to issues of concern to patients. The panel uses established criteria to assign an overall impact/priority score to each proposed study. Criteria usually include study significance, investigators' qualifications, innovation, scientific approach, and research environment. The panel also may be asked to evaluate the application using other criteria, such as advocate or community participation in the design and implementation of the project; protection of human subjects and vertebrate animals; biohazards; and inclusion of women, minorities, and children; as well as appropriateness of budget and period of support. The second tier of review typically is performed by an advisory board that may include nongovernmental scientists, grant program administrators, and, for some programs and agencies, community representatives. This advisory board reviews the proposals recommended by all agency peer review panels for their scientific merit and relevance to the agency's priority programmatic goals. In deciding which grant applications to fund, agency leadership considers the recommendations from the first and second tiers of review along with other information, such as identified gaps in the agency's portfolio.

7.2.1 National Institutes of Health

The Committee's analysis of the NIH portfolio included all projects funded by NIH's 27 ICs, several of which conduct and/or support some breast cancer research. The Committee identified 2,910 projects funded by NIH ICs from fiscal years (FY) 2008 to 2010 that focused primarily on breast cancer (see Appendix 4 for more details about methods used in this analysis).

Breast cancer research receives more NCI funding than research on any other cancer. NCI reported spending more than $631 million in FY2010 on breast cancer research.

NCI is the nation's principal agency for cancer research and the world's largest organization dedicated solely to cancer research. NCI utilizes its intramural research program and research grants to study the causes, prevention, detection, diagnosis, and treatment of cancer through numerous research projects and clinical trials. Breast cancer research receives more NCI funding than research on any other cancer. NCI reported spending $631.2 million in FY 2010 on breast cancer research, more than twice the amount spent on the next most-funded cancer.[a] NCI currently supports more than 1,500 active clinical trials for breast cancer alone. In addition, NCI supports a nationwide network of Comprehensive Cancer Centers and regional Cancer Centers. These NCI-designated Cancer Centers are a major source of research on the nature of cancer and effective approaches for cancer prevention, diagnosis, and therapy. These Centers also deliver new medical treatments to patients and their families, educate health-care professionals and the public, and reach out to underserved populations.

[a] See http://www.cancer.gov/cancertopics/factsheet/NCI/research-funding

To estimate the population burden from cancer and to assess the success of its research program, NCI conducts surveillance of cancer morbidity and mortality as well as cancer-related behaviors and risks in populations, cancer-related health services, and cancer outcomes. NCI also funds and manages the Surveillance, Epidemiology, and End Results (SEER) Program to collect, analyze, and disseminate cancer mortality, incidence, and survival data to support research and public health decision making. The cancer registries that are funded to collect, analyze, and disseminate data for SEER, cover approximately 28 percent of the U.S. population. To monitor health behaviors, services, and outcomes, NCI develops and supports special or ongoing surveys of the general population (e.g., cancer-related modules in CDC's National Health and Nutrition Examination and National Health Interview surveys) and health providers (for example the Survey of Physician Attitudes Regarding the Care of Cancer Survivors [SPARCCS]). NCI also develops resources for population research, such as Population-Based Research Optimizing Screening through Personalized Regimens (PROSPR), to increase understanding of ways to improve the screening process for breast, colon, and cervical cancer. Another NCI resource is the Breast Cancer Surveillance Consortium (BCSC), which was established to support studies that assess the delivery and quality of breast cancer screening and related patient outcomes as well as the etiology of breast cancer and breast conditions, in the United States. The BCSC is collaborative network of seven mammography registries with linkages to tumor and/or pathology registries. This Consortium has led to improved understanding of the role of mammographic density (measured through mammography); family history of breast cancer; and reproductive, pharmacologic, and other factors in the risk of breast cancer and its subtypes.

NIEHS is the nation's principal agency for research related to understanding ways in which the environment influences the development and progression of human disease. NIEHS is the headquarters for the National Toxicology Program (NTP), an interagency program that involves NIH, CDC, and FDA. The NIEHS intramural research program supports epidemiologic studies of environmentally associated diseases including breast cancer, as well as toxicological testing of environmental substances and intervention and prevention studies to reduce the effects of exposures to hazardous environments. The NIEHS also supports a large portfolio of research grants that span the range from mechanistic research, animal disease models and systems, to clinical and epidemiologic studies.

A significant portion of the NIEHS research portfolio is relevant to breast cancer and the environment, although breast cancer might not be the primary health outcome in many projects. The total amount of research dollars that the NIEHS spends on breast cancer and environment research, therefore, is difficult to ascertain accurately. The NIEHS allocates a portion of its grant support specifically to breast cancer and the environment research. The portion of NIEHS grant support specifically relevant to breast cancer and the environment was included in the portfolio analysis.

The Committee identified breast cancer research that is under way in other NIH Institutes, including the:

- National Institute of General Medical Sciences (NIGMS),
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK),
- National Heart, Lung, and Blood Institute (NHLBI),
- National Institute of Biomedical Imaging and Bioengineering (NIBIB),
- National Center for Advancing Translational Sciences (NCATS), formerly the National Center for Research Resources (NCRR),
- National Human Genome Research Institute (NHGRI),
- National Institute on Aging (NIA),

- Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and
- National Center for Complementary and Alternative Medicine (NCCAM).

According to the RePORT system, the NIH spent almost $2.4 billion on breast cancer research in FY 2008 to 2010,[b] with approximately 83 percent of this funding administered by the NCI, 5 percent by the NIEHS, and 2 percent or less by each of the other ICs.

Although the extensive NIH research portfolio includes grants focused on breast cancer and the environment, the NIH does not have a specific approach for identifying and classifying this type of research across all ICs. The NCI, however, uses the CSO to code all of its grants and many of the cancer-related grants of collaborating ICs. This coding can be used to assess breast cancer research activities across ICs. Figure 7.1 shows the distribution of projects related to breast cancer across the NIH ICs by CSO category.[c] The "projects" included in this figure are: (1) intramural research projects, (2) research centers, (3) extramural research projects, (4) small business innovation research (SBIR) and small business technology transfer studies (STTR), (5) training (institutional and individual) projects, (6) research and development (R&D) contracts, (7) interagency agreements, and (8) other research projects (research grants not classified as research projects or research centers). Many projects are relevant to multiple CSO categories; hence, a single project may be represented in multiple categories in Figure 7.1.

The CSO uses 39 subcategories, and three of these categories were used by the Committee to identify grants with an environmental focus. These are CSO Etiology Code 2.1: *Exogenous Factors*, CSO Etiology Code 2.3: *Interactions of Genes and/or Genetic Polymorphisms with Exogenous and/or Endogenous Factors*, and CSO Prevention Code 3.1: *Interventions to Prevent Cancer: Personal Behaviors that Affect Cancer Risk*. The Committee considered environmental health research to include projects with any or a combination of these three codes (Figure 7.1). Etiology studies (Codes 2.1 and 2.3) focus on understanding factors that lead to cancer by examining basic biological mechanisms that result in cancer and factors in human populations that increase cancer risk. Prevention studies (Code 3.1) use knowledge derived from etiology studies in laboratory studies and human behavior and social science research to develop and test ways to prevent cancer. Twenty-seven percent of NIH breast cancer research projects for FY 2008 to 2010 were relevant to the major etiology and/or prevention CSO categories (Codes 2.0 and 3.0) but only about 10 percent could be classified into the combined "environmental health research" category (Codes 2.1, 2.3, 3.1). Based on this analysis, only 301 NIH-funded breast cancer projects had some focus on environmental health research, representing a maximum investment of 16 percent[d] of the breast cancer budget for the fiscal years examined.

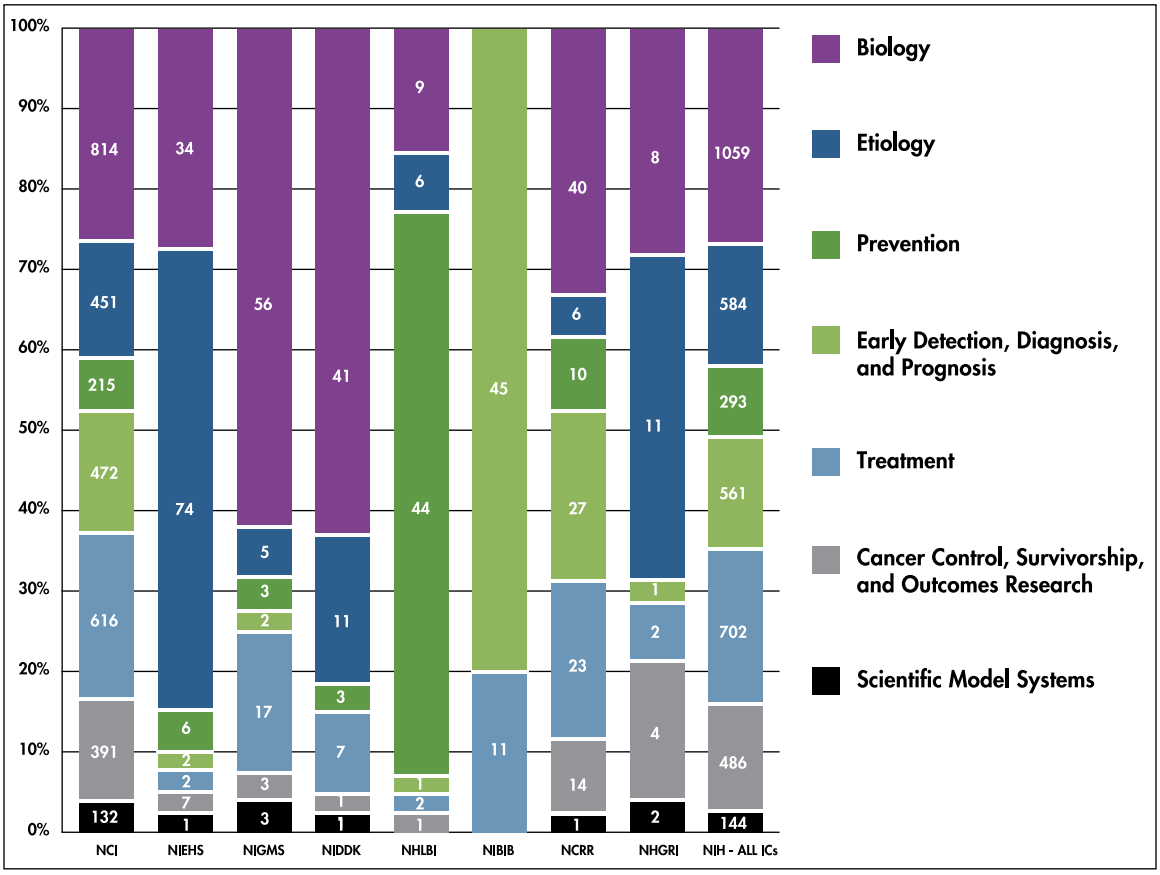
7.2.2 Department of Defense

Initiated in FY 1992, the DOD Breast Cancer Research Program (BCRP) received congressional appropriations totaling nearly $2.8 billion through FY 2012 to fund innovative, high-impact breast cancer research. The BCRP created unique award mechanisms to support a broad portfolio of investigator-initiated research activities that foster synergistic, multidisciplinary collaborations. For fiscal years 2006 to 2010, approximately $610 million BCRP research dollars were allocated to the following major funding categories (see Figure 7.2):

- **Career Development grants** to outstanding individuals in the predoctoral and postdoctoral stages of training in breast cancer research and grants to train investigators at institutions that do not have an established breast cancer research program;

[b] See http://report.nih.gov/rcdc/categories/ (put breast cancer in the search box).
[c] See https://www.icrpartnership.org/CSO.cfm for descriptions of CSO categories.
[d] This percentage indicates the maximum proportion of the budget because some projects fell into more than one CSO category, and budgets are not divided by CSO category.

Figure 7.1. Distribution of NIH IC spending on projects related to breast cancer by CSO categories (FY 2008-2010)

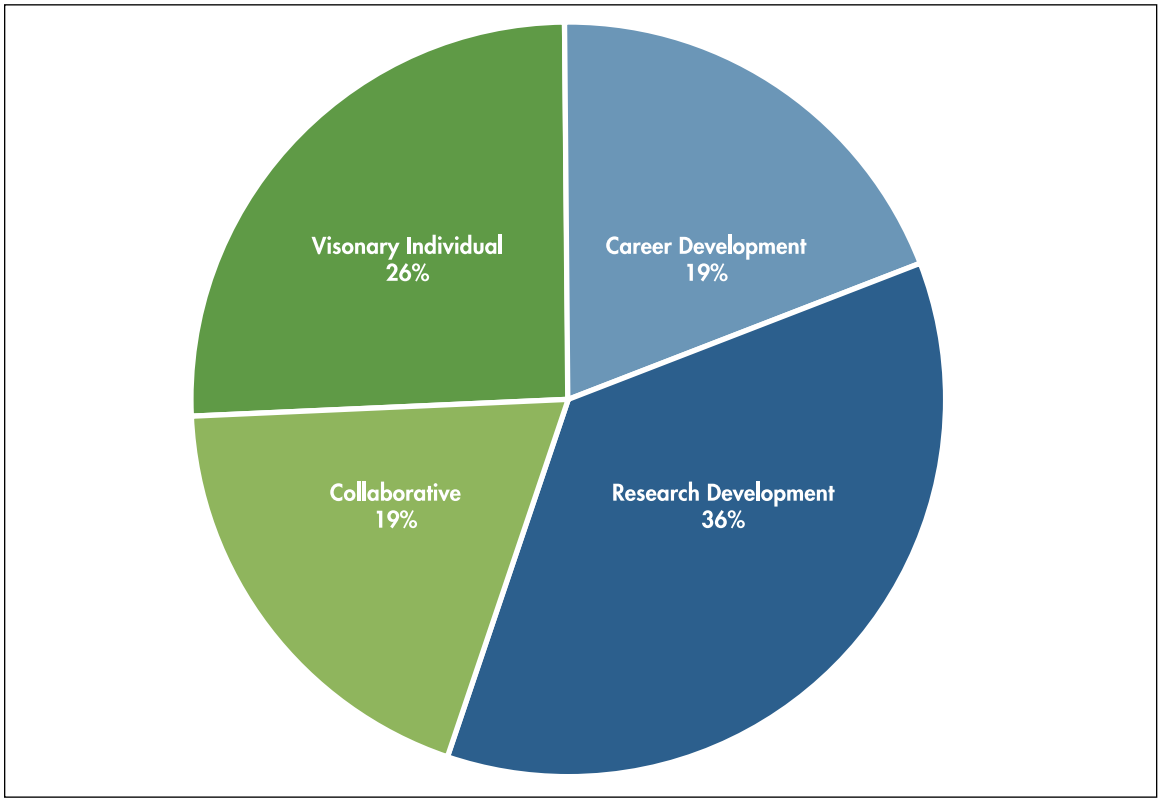


One vertical bar is drawn for each of the ICs. Colors within each bar represent the different CSO categories. For each IC, the size of the color bar indicates the proportion of breast cancer projects in the corresponding CSO category, whereas the number within the color bar indicates the proportion of projects in that category. This figure shows ICs that funded 1 percent or more of the total NIH breast cancer research. Relative to other ICs, substantially more projects in every category were funded by NCI, but the largest number fell into the Biology category (814 projects). The largest number of NIEHS-funded projects fell into the Etiology category (74 projects). For NIGMS, NIDDK, and NCRR, the largest category was Biology (56, 41, and 40 projects, respectively). For NHLBI, the largest category was Prevention, but many of the 44 projects in this category were explained in part by the inclusion of the Women's Health Initiative (WHI), which examines cardiovascular disease, cancers of the breast and colon/rectum, and osteoporosis, the most common causes of death, disability, and impaired quality of life in postmenopausal women. Most NIBIB breast cancer projects (45) focused on Early Detection, Diagnosis, and Prognosis. The largest category for NHGRI was Etiology (11 projects), which was followed closely by Biology (8).

- **Research Development,** which includes investigator-initiated grants spanning the research pipeline, including concept building, idea development, translational, and clinical research;
- **Collaborative grants** that require partnerships among scientists with synergistic expertise, as well as breast cancer advocates; and
- **Visionary Individual grants** to support individuals with a demonstrated history of innovation and leadership in the pursuit of novel, innovative ideas with a vision toward the eradication of breast cancer.

Figure 7.3 shows that approximately 75 percent of DoD BCRP funding is for basic biology and treatment research, with only 3 percent for prevention and cancer control projects. Note that, unlike the NIH, DoD grant funding is broken down by dollar amount in a given CSO category, so Figure 7.3 presents proportions of funding rather than proportions of

Figure 7.2. Distribution of approximately $610 million in DoD BCRP funding by grant category for FY 2006 to 2010



The largest proportion of funding went to Research Development grants (36%), followed by Visionary Individual grants (26%). Collaborative grants and Career Development grants each comprised 19 percent of BCRP funding.

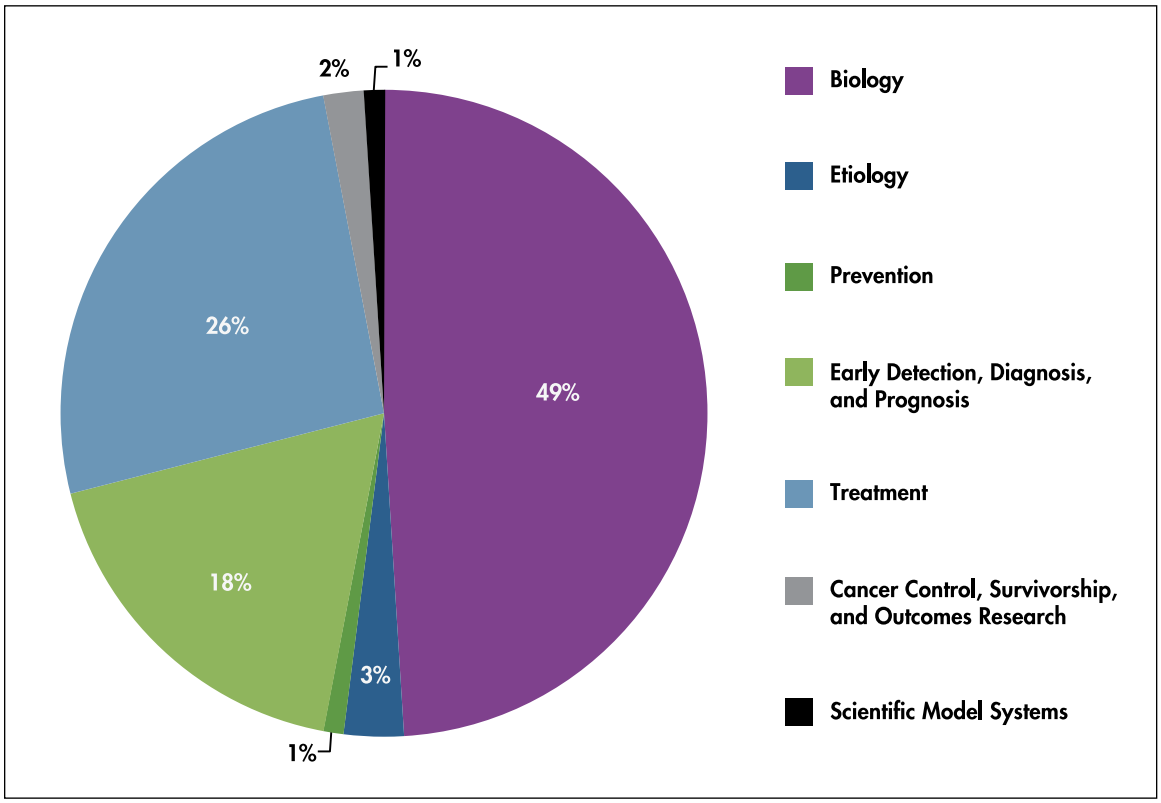
grants. The DoD BCRP does not specifically solicit (or target) research with an environmental focus, but the agency research grant portfolio includes studies of breast cancer and the environment. A total of 162 BCRP awards from FY 2006 to 2010 were classified as "environmental health research" using the same definition applied to NIH projects. Environmental health research, therefore, represents approximately 10.8 percent of DoD's funded breast cancer projects in our analysis.

7.2.3. Centers for Disease Control and Prevention

The CDC's Division of Cancer Prevention and Control (DCPC) conducts and supports studies, often in collaboration with partners, to develop and apply sound science to reduce the burden of breast and other cancers and eliminate health disparities. This research applies many different areas of expertise (behavioral science, economics, epidemiology, health services, medicine, and statistics) to meet the public health needs identified by DCPC programs, health care providers, people affected by cancer, and the larger comprehensive cancer control community. Other CDC offices that conduct breast cancer-related research include the National Center for Environmental Health, the National Institute for Occupational Safety and Health (NIOSH), and the Agency for Toxic Substances and Disease Registry (ATSDR).

CDC does not have a dedicated appropriation or budget line for cancer research; however, portions of funding from all of CDC's cancer budget lines are used to support applied research. This research often is related to crosscutting issues that may affect multiple cancers. The CDC brings a public health perspective to cancer.

Figure 7.3. Distribution of DoD breast cancer research funding by CSO category in percent of total dollars awarded for FY 2006 to 2010



Almost one-half of DoD funding (49%) went to research in the Biology category. More than one-quarter (26%) went to research in the Treatment category. The next largest proportion of funding (18%) went to research in the Early Detection, Diagnosis, and Prognosis category. Three percent of funding went to research in the Etiology category, and 2 percent went to the Cancer Control, Survivorship, and Outcome Research category. Only 1 percent of funding went to research in the Prevention category.

The CDC's applied research fills specific gaps by conducting cancer prevention and control research that:

- Informs public health activities, programs, and policies;
- Promotes the translation of scientific knowledge into practice;
- Provides an improved understanding of cancer patterns and trends;
- Identifies unmet needs for public health action;
- Provides insights applicable to the control of all cancers;
- Assists in developing educational strategies and materials for providers and the public about cancer screening; and
- Guides the development of quality-assurance procedures.

The CDC supports the Cancer Prevention and Control Research Network (CPCRN), which is comprised of 10 Prevention Research Centers. This network was established in partnership with the NCI to support the conduct of research relevant to local cancer prevention and control needs and promote the translation of research into public health practice. The CPCRN conducts community-based, participatory research across its 10 centers; some of this research addresses issues relevant to breast cancer control.

As part of the Patient Protection and Affordable Care Act of 2010, the CDC was directed to develop activities designed to prevent and control breast cancer in young women. The CDC is conducting a number of research, programmatic support, and communication projects focused on the development of appropriate and effective health communication messages

in this area. These projects will identify effective communication methods, identify young women with a high risk of developing breast cancer, develop policies and communication strategies to educate these women about breast cancer risk, and provide support services for young breast cancer survivors.

The CDC's National Breast and Cervical Cancer Early Detection Program (NBCCEDP) supports programs in all 50 states, the District of Columbia, five U.S. territories, and 12 tribes to provide clinical breast exams, mammograms, and related diagnostic tests to low-income, uninsured, underinsured, and underserved women. Programs also conduct patient navigation, case management, public education, client recruitment, quality assurance, and program evaluation activities to increase and improve breast screening among priority populations. As a result of the NBCCEDP, more than 35,000 breast cancers have been diagnosed to date. In support of this program, research is under way to identify methods for reaching minority women, geographic disparities in mammography capacity, and transportation barriers to mammography.

CDC's National Center for Environmental Health supports the National Environmental Public Health Tracking Network (Tracking Network), a system of integrated health, exposure, and hazard information and data from a variety of national, state, and city sources. The Tracking Network makes maps, tables, and charts available based on data about chemicals and other substances found in the environment, as well as data on selected chronic diseases and conditions. The Tracking Network offers data on breast cancer incidence from 2001 to 2008 for most states and counties.

CDC's National Center for Environmental Health, Division of Laboratory Sciences (DLS), measures more than 350 environmental chemicals and nutritional indicators in people's blood and urine to identify unsafe exposures or nutritional deficiencies. DLS uses high-quality measurements in participants of the National Health and Nutrition Examination Survey (NHANES) to assess population exposures and provides biomonitoring measurements in more than 50 collaborative studies per year of environmental exposures and adverse health effects, including breast cancer. DLS is applying its unique analytical capabilities by conducting environmental agent and biomarker analyses on the samples collected by the NCI and NIEHS through the Breast Cancer and the Environment Research Project (BCERP). The purpose of this collaborative effort is to study the effects of environmental factors on the age of onset and progression through puberty of a diverse population of pre- and peripubertal girls in the United States. Priority biomarkers and environmental agents being studied include phytoestrogens, phthalates, alkyl phenols (bisphenol A, BPA), hydroxypyrene, persistent organohalogens, metals, and cotinine.

CDC's ATSDR is planning a study to investigate the possible association between increased risk for male breast cancer and exposure to volatile organic compounds (VOCs) in drinking water at Marine Corps Base Camp Lejeune in North Carolina. Major chemical contaminants found in the Camp Lejeune drinking water included trichloroethylene (TCE), tetrachloroethylene (PCE), compounds formed from the degradation of PCE and TCE in ground water—t-1,2-dichloroethene (DCE) and vinyl chloride (VC)—and refined petroleum products (e.g., benzene). Exposure to these VOCs can cause a variety of illnesses, including cancer. Cases of male breast cancer and a random sample of controls with cancers unrelated to VOC exposure who all had the potential to be exposed to contaminated drinking water at Camp Lejeune will be identified from cancer registries and treatment records obtained from the U.S. Department of Veterans Affairs (VA). The planned study combines data from personnel military records, cancer registry and treatment records, and estimated historical levels of VOC contaminants in the drinking water supply.

The CDC also conducts and supports breast cancer research through its extensive surveillance activities, including the:

- **National Program of Cancer Registries (NPCR),** which collects information about cancer incidence in the United States through state-based cancer registries. This information is used in breast cancer research and to answer community questions and concerns about cancer.

- **Behavioral Risk Factor Surveillance System (BRFSS),** which is the world's largest ongoing telephone health survey system that gathers information by state on health risks in the United States. Information about exercise, diet, smoking, alcohol, family history of breast cancer, breast cancer screening, and other factors is collected.

- **National Health Interview Survey (NHIS),** which collects information about many different kinds of diseases and how they affect people's lives. The survey also collects information about breast cancer screening and risk factors. NIH ICs provide substantial support for this survey.

- **National Health and Nutrition Examination Survey (NHANES)**, which is a continuously conducted, nationally representative examination survey of children and adults, collects data on a wide range of factors including diet, physical activity, health behaviors, and biomarkers related to these factors as well as levels of a large number of environmental exposures in blood and urine. NIH ICs also provide substantial support for this survey.

7.2.4 U.S. Environmental Protection Agency

Research at the EPA is conducted through its many research laboratories. The Office of Research and Development manages seven national research laboratories and centers that develop knowledge and scientific tools to support EPA's environmental standards and assessments. The Office of Air and Radiation and the Office of Chemical Safety and Pollution Prevention manage seven additional research laboratories that support regulatory implementation, compliance, and enforcement at a national level. Finally, each of EPA's 10 regional offices supports research laboratories that gather data and perform analyses for regional decision making.

EPA's research mission includes providing the fundamental science for understanding and predicting chemically based health risks, including cancer risks. Although the EPA does not have a research program that specifically targets breast cancer as a health outcome, the agency is developing and evaluating new screening and testing approaches as recommended in the National Academy of Science's National Research Council (NRC) report, *Toxicity Testing in the 21st Century, A Vision and a Strategy.*[2] These approaches focus on defining cellular and molecular pathways of toxicity, including those that may be associated with cancer causation. (For more information about these strategies, see Section 7.3.4 and visit www.epa.gov/research/docs/css-strap.pdf). These issues have relevance to breast cancer etiology related to environmental exposures.

EPA's research objectives include the development and implementation of the Endocrine Disruptor Screening Program, which is designed to test substances for their potential to disrupt the endocrine system. Specifically, the goals of the program are to validate testing systems (including both *in vivo* and *in vitro* models) and accumulate evidence to determine whether certain substances, alone or in combination, may alter hormone production or action. These goals have relevance to breast cancer and the environment based on research linking endocrine disrupting compounds (EDCs) to breast cancer risk (see Chapter 6.2.6). Additional EPA research focuses on mechanisms through which EDCs, such as environmental estrogens and anti-androgens, might affect reproductive tract development and the timing of puberty, both of which also have implications for breast cancer risk.

The EPA is exploring the use of cell-based, high-throughput screening assays to determine the ability of chemicals (and chemical combinations) to activate a variety of molecular pathways of toxicity, including those predictive of cancer initiation. EPA's National Center for Computational Toxicology (NCCT) supports

the ToxCast program that develops tools and protocols to support large-scale *in vitro* screening of chemicals. This program is one of EPA's contributions to the collaborative Tox21 program (discussed in Section 7.3.4), as well as the Endocrine Disruptor Screening Program. NCCT also supports the Aggregated Computational Toxicology Resource (ACToR), an online warehouse of all publicly available chemical toxicity data that can be used to gauge potential chemical risks to human health and the environment. ACToR aggregates data from more than 1,000 public sources on more than 500,000 environmental chemicals and is searchable by chemical name and other identifiers and by chemical structure. ACToR allows users to search and query physical-chemical values and *in vitro* and *in vivo* toxicology data from multiple EPA programs, including ToxRefDB (animal toxicity studies), ToxCastDB (ToxCast screening results), ExpoCastDB (human exposure and factor data for chemical prioritization), and DSSTox (high-quality chemical structures).

7

EPA's ToxCast and NIH's National Toxicology Program are developing new ways to test chemicals implicated in breast cancer.

7.2.5 U.S. Food and Drug Administration

Science is the foundation of the FDA's regulatory decision-making process that protects and promotes the health of U.S. consumers. The FDA's mission is to protect and advance public health by helping to speed innovations that provide the nation with safe and effective medical products and that ensure food safety.[e] FDA research continually explores ways that the latest knowledge and technology can be applied to its regulatory challenges. FDA research is translational, linking basic and applied research to respond to premarket or postmarket product concerns.

The FDA recently developed a new strategic plan for regulatory science, the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products.[f] In addition, the FDA funds an intramural research program, an extramural research grant program, a set of special funding initiatives that target specific knowledge gap areas, and a set of workforce development initiatives to support recruitment of professionals to address women's health issues.[3]

The FDA supports an Office of Women's Health (OWH) as part of its Research and Development Program to examine gaps in current scientific knowledge related to women's health, encourage new research directions in this area, and help establish new standards of excellence. The OWH also funds scientific research, workshops, and training to support sound policy development and decision making related to women's health. Initiatives include an investigation of possible enhanced exposure of women to estrogens, phytoestrogens (estrogen-like chemicals from plants), and xenoestrogens (estrogen-like synthetic chemicals) through cosmetic products. The FDA's Office of Cosmetics and Colors also conducts minimal research on exposures to and the safety of chemicals used in cosmetics and personal care products.

In addition, the FDA coordinates research on radiation imaging through the FDA Center for Devices and Radiological Health in the Office of Medical Products and Tobacco. FDA certifies mammography facilities and regulates the standards for the mammography machines and the training for the people who provide mammograms.

At the FDA's National Center for Toxicological Research (NCTR), interdisciplinary scientific experts conduct animal or cell-based research to evaluate the biological effects of potentially toxic chemicals or microorganisms; define the complex mechanisms that govern their toxicity; and understand critical biological events related to exposure, susceptibility, and risk. FDA/NCTR scientists are conducting numerous

[e] See http://www.fda.gov/ScienceResearch/AboutScienceResearchatFDA/default.htm.
[f] See http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm268095.htm.

studies to understand the molecular basis of the efficacy and safety of drugs and other consumer products and how genetics, sex, diet, and other environmental factors influence that efficacy and safety. The Center also develops, refines, and applies current and emerging technologies to improve safety evaluations. Although the NCTR does not have a program specifically directed at breast cancer, it collaborates with the OWH to support a better understanding of women's health issues, including breast cancer. For example, one NCTR study assesses tamoxifen safety and toxicity and its effect on cancer risk. Another study develops methods for associating genetic variation with breast cancer. The NCTR also collaborates with the NTP to test chemical effects over multiple generations. Chapter 6 discusses findings from the NCTR/NTP report demonstrating that male mammary glands are highly sensitive to exposures to genistein and ethinyl estradiol during developmental periods.[4] More information about NCTR studies and their findings can be found in the Center's annual reports and Research Highlights, which are available at http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/WhatWeDo/default.htm.

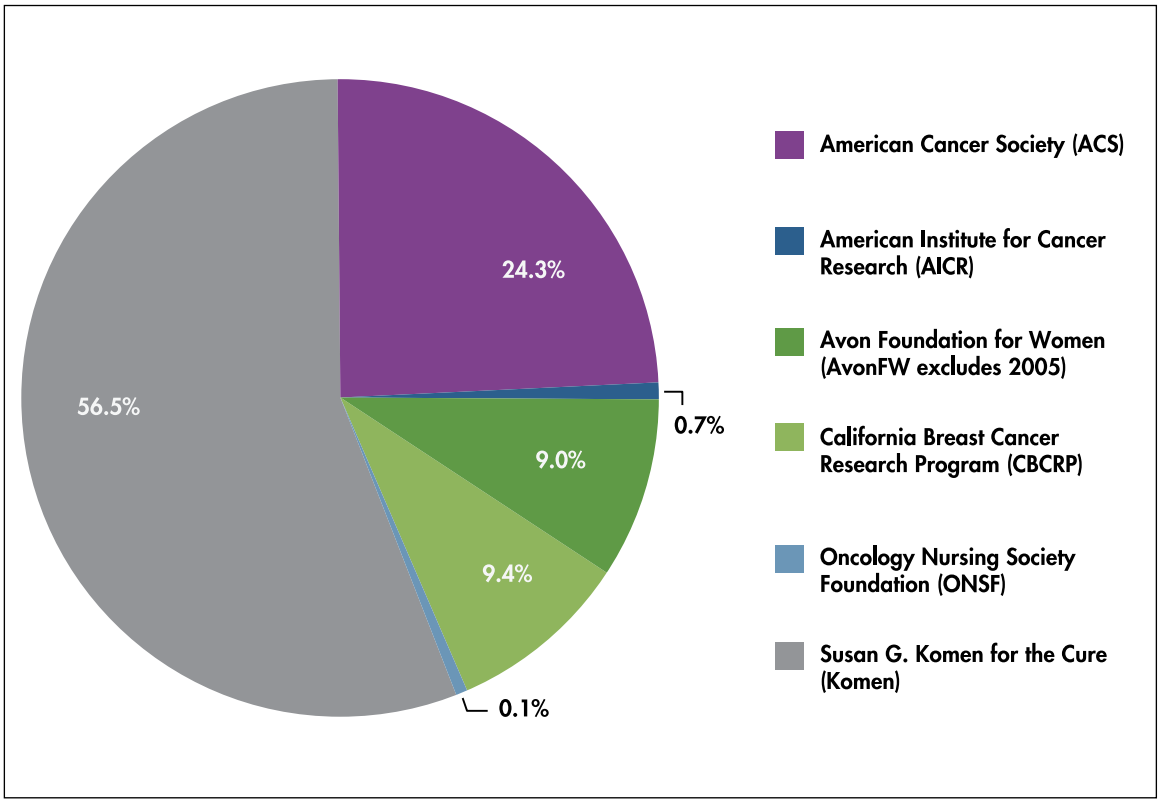
7.2.6 Nongovernmental and State Organizations

Although federal agencies provide the majority of breast cancer research funding, nongovernmental organizations (NGOs) and certain state-funded organizations provide substantial funding for research on breast cancer and the environment. The Committee obtained information on numbers of NGO grants and grant funding from the ICRP (which excluded some NGOs and state-funded organizations). Breast cancer research funding totaled $1.66 billion for six major NGOs for FY 2005 to 2009 (Avon Foundation for Women data are unavailable for FY2005.) The Susan G. Komen for the Cure foundation provided more than half of this total (see Figure 7.4). Compared with federal agencies, percentages of NGO research funding for breast cancer treatment and biology were relatively low, at only about 18 percent and 25 percent, respectively (Figure 7.5). The analysis of ICRP information showed that cancer control, prevention, and detection research made up roughly 40 percent of NGO expenditures. Breast cancer research specifically coded to prevention comprised less than seven percent of total NGO breast cancer grant funding.

The same basic funding mechanisms used by the federal agencies are used by cancer NGOs and state organizations, with the majority of grant programs funding investigator-initiated or targeted research. This section provides several examples of NGOs and one state-funded organization that support breast cancer research, including research that improves our understanding of environmental influences on breast cancer.

- **American Cancer Society (ACS):** Entering its 100th year of providing support for cancer research and services to cancer patients, survivors, and their families, the ACS supports breast cancer research through intramural and extramural programs. Intramural research supports epidemiology studies, health services research, tobacco control studies, and research on patient and survivor behaviors. ACS also collaborates with the CDC and NCI to produce annual statistics on cancer mortality, incidence, and survival. Major epidemiology research at the ACS includes the Cancer Prevention Studies, a set of large, long-term prospective cohort studies of the environmental factors associated with increased cancer risk. These studies have been particularly valuable in helping to elucidate the role of health behaviors such as alcohol and tobacco use, diet and physical activity, reproductive factors, genetic factors, and personal susceptibility factors such as obesity in breast cancer susceptibility. The ACS extramural grant program funds investigator-initiated research projects for early career scientists and postdoctoral fellows, individual and block training and education grants, career recognition awards, and targeted research in cancer control and health disparities.

Figure 7.4. Distribution of breast cancer research grant funding by major NGOs (FY 2005-2009)

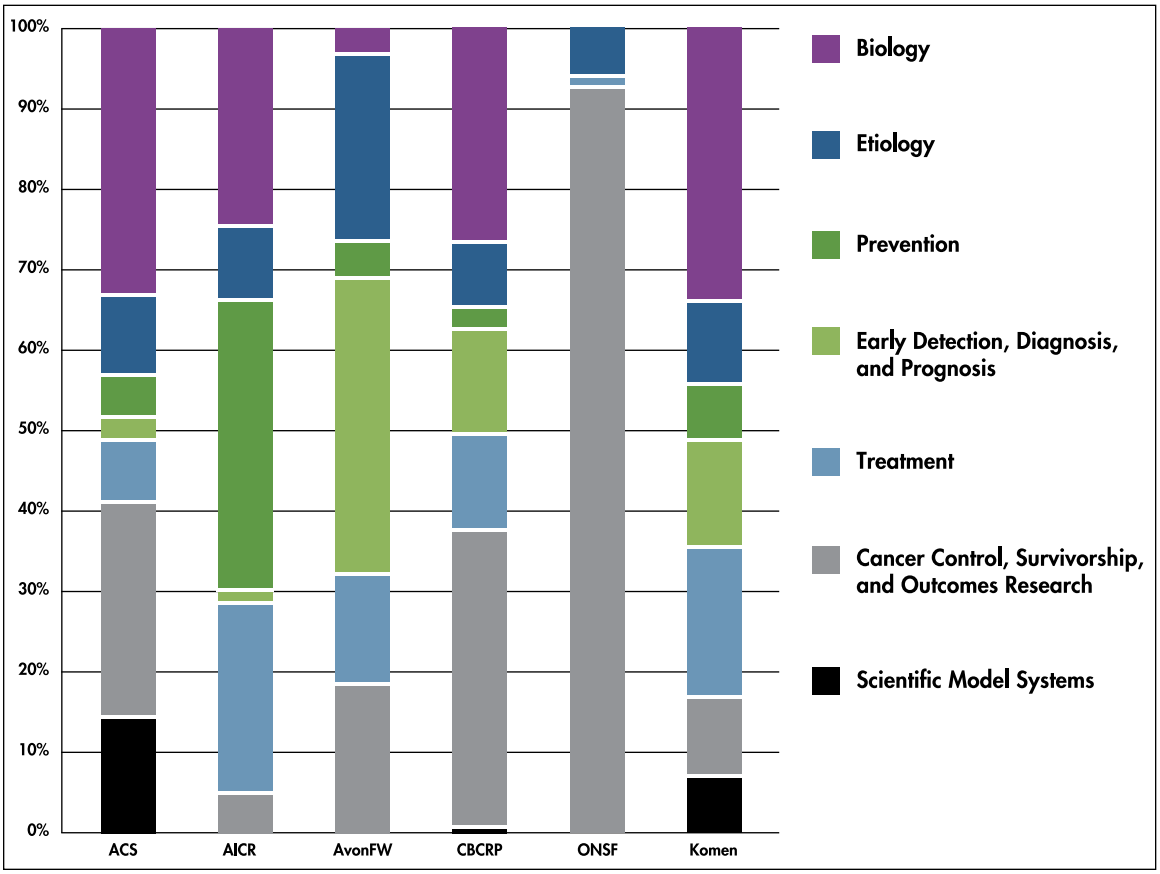


More than one-half of this funding (56.5%) was provided by Susan G. Komen for the Cure. Nearly one-quarter of this funding was provided by ACS. CBCRP provided slightly more than 9 percent of this funding. The AvonFW provided 9 percent of the funding (excluding FY 2005). The AICR and ONSF each funded less than 1 percent of the total. An important limitation of ICRP NGO data is the inconsistent reporting time-frame. One organization may report within 6 months, another within 1 or 2 years.

- **American Institute for Cancer Research (AICR):** The AICR funds research in the fields of nutrition; physical activity; and cancer prevention, treatment, and survival, with the goal of providing practical tools and information to help people prevent and survive many types of cancer. The AICR continually updates *Food, Nutrition and the Prevention of Cancer: A Global Perspective*, first published in 1997.

- **Avon Foundation for Women (AvonFW):** Avon Foundation research programs focus on understanding the causes and prevention of breast cancer. The AvonFW funds human studies on the role of environmental factors, including viruses and infectious agents, on breast cancer risk. The AvonFW also supports research to validate biomarkers, clinical assays, and diagnostic tests that predict breast cancer risk or that can be used to monitor changes in the healthy breast over time. Through a partnership with the Dr. Susan Love Research Program, the AvonFW is supporting the Love/Avon Army of Women program. A goal of this program is to recruit one million healthy women of every age and ethnicity, including breast cancer survivors and women at high-risk for the disease, to provide information about themselves and receive information about studies that are seeking research subjects. The NIEHS Sister Study was one of the first research studies supported by the Love/Avon Army of Women (see Section 7.3.3). The AvonFW also has provided support for the BCERP and its predecessor initiative, the Breast Cancer and the Environment Research Centers (BCERCs), described in Section 7.3.2.

Figure 7.5. Distribution of projects related to breast cancer across NGOs by CSO categories (FY 2005 to 2009)



One vertical bar is drawn for each of the six NGOs. Colors within each bar represent the different CSO categories. For each NGO, the size of the color bar indicates the proportion of breast cancer projects in the corresponding CSO category. Komen and ACS funded the majority of projects, with similar proportions of biology, etiology, and prevention studies. A larger proportion of ACS-funded projects focused on cancer control and scientific model systems, whereas a larger proportion of Komen projects focused on treatment and early detection. A large proportion of AvonFW projects focused on detection, whereas AICR funded mostly prevention projects. The ONSF projects are, for the most part, related to cancer control, survivorship, and outcomes research.

- **Oncology Nursing Society Foundation (ONSF):** The ONSF research program provides financial support for projects that increase the knowledge base for oncology nursing practice and that train future oncology nurse researchers. Funding preference is given to projects that involve nurses in the design and conduct of studies that promote theoretically-based oncology practice. More than 90 percent of ONSF research funding supports cancer control, survivorship, and outcomes studies. The ONSF also provides limited support for cancer etiology research.

- **Susan G. Komen for the Cure:** This foundation supports research that will identify and deliver cures for breast cancer. Komen uses four funding mechanisms. Promise grants fund transdisciplinary research focusing on late (5 or more years after diagnosis) breast cancer recurrence. Fellowship and training grants are used to bring new scientists into breast cancer research. Career catalyst research grants allow scientists in the early stages of their careers to achieve research independence. Komen also funds investigator-initiated research with specific scientific goals, such as prevention and early detection.

- **California Breast Cancer Research Program (CBCRP):** The CBCRP, funded by donations on California State income tax forms to the Breast Cancer Research Fund and administered by the University

- of California, was created to support innovative, collaborative breast cancer research and communication in the California scientific and lay communities. This program funds research concerning community impacts of breast cancer as well as on breast cancer etiology, prevention, detection, prognosis, and treatment. Special research initiatives fund studies to identify and eliminate environmental causes of and disparities in breast cancer. The CBCRP makes detailed information about funded grants on breast cancer and the environment available online at http://cbcrp.org.127.seekdotnet.com/research/byResearchPriority.asp.

  Although California represents the largest state-funded breast cancer research effort in the nation, other states have programs that target public funds to support breast cancer research and services for breast cancer survivors. Examples include the Illinois Penny Severns Breast, Cervical and Ovarian Cancer Research Fund[g] and the Pennsylvania Breast and Cervical Cancer Research Fund.[h] Because of the limited information available about other breast cancer research state funding, we were unable to assess state funds directed toward breast cancer and the environment research. Goals for funding breast cancer research and support for breast cancer survivors, however, are major components of every state's comprehensive cancer control plan. Comprehensive cancer control plans are developed by communities and their partners to pool resources to reduce the burden of cancer.

7.2.7 Portfolio Analysis Summary

In summary, a number of governmental and nongovernmental organizations conduct and/or support research on breast cancer and the environment. Principal agencies that support or conduct research in this area are the NCI and NIEHS at NIH, and the DoD's congressionally directed BCRP. The portfolios of these agencies span basic biological research through population research. The CDC focuses on surveillance of breast cancer risk factors and environmental exposures. Regulatory agencies, including the FDA and EPA, undertake research related to environmental exposures that fall within their mission and inform the regulatory process. The largest sources of NGO funding for research on breast cancer and the environment come from Susan G. Komen for the Cure and the AvonFW. The ACS supports training and research grants focused on cancer control and population science as well as surveillance.

Our research portfolio analysis pointed out relatively low levels of federal and NGO funding for breast cancer prevention and etiology research.

The Committee found that only about 10 to 11 percent of breast cancer research projects funded by the NIH and DoD focused on environmental health during the fiscal years examined. The NIH support for projects relevant to breast cancer and the environment, however, is only an estimate. For the other federal agencies, the Committee could not measure their exact investment in the study of breast cancer and the environment because of differences in how research is coded across organizations. At this time, no specific efforts are being made to coordinate federal and nongovernmental research on breast cancer and the environment.

The research portfolio analysis highlights the relatively low level of federal and NGO funding for breast cancer prevention and etiology research. Low funding levels in this area may be a result of a research funding strategy that is more focused on developing cures rather than on prevention.[5] This small proportion of projects focusing on breast cancer prevention and etiology, however, is partly the result of the low number of applications submitted in these areas. The Committee was disappointed to learn that both the DoD and NIH do not receive large numbers of grant applications in these areas relative to the number of applications focused on basic research and treatment, in spite of the fact that the award mechanisms accept all types of research.

[g] See http://www.idph.state.il.us/about/womenshealth/fund.htm.
[h] See http://www.portal.state.pa.us/portal/server.pt/community/cancer/14165/breast_and_cervical_cancer/557842.

This finding highlights the need to increase the number of applications submitted for studies of environmental factors that influence breast cancer risk and to prioritize funding for projects focusing on etiology and prevention. The nation needs research that supports effective risk-reduction activities to decrease the incidence of breast cancer.

7.3 Research Collaborations

In addition to the portfolio analysis of grants, the Committee identified a large number of collaborations among federal agencies, and between federal agencies and NGOs, with relevance to research on breast cancer and the environment. Some of these collaborations are congressionally mandated, but most are integral parts of the research mission of the federal agencies. This section includes examples of productive collaborative efforts that have, continue to have, or potentially have a large impact on our understanding of the role of environmental factors in breast cancer. Some of these efforts were initiated recently and may not have findings at this point in time.

7.3.1 Research Infrastructure

- **National Toxicology Program (NTP):** The NTP is an interagency program that involves the NIH, CDC, and FDA and is headquartered at the NIEHS. This program was established in 1978 to coordinate toxicology testing programs within the federal government; strengthen the science base in toxicology; develop and validate improved testing methods; and provide information about potentially toxic chemicals to health, regulatory, and research agencies; scientific and medical communities; and the public. The NTP provides a platform for testing the ability of substances to affect cancer and noncancer end points. Specifically, the Program tests substances for their ability to act as carcinogens in rodent models. Just more than 2,500 chemicals have been studied and, as of September 2011, 616 chronic rodent cancer studies (2-year bioassays) had been conducted. Within those studies, numerous test compounds demonstrated clear (n = 214) or some (n = 41) evidence of carcinogenicity in female rodents. The *Report on Carcinogens* (RoC), a biannual report written by the NTP since 1980, provides a cumulative description of the carcinogenicity status of more than 240 chemicals/chemical classes.[6] When chemicals of interest are deemed to show evidence as mammary gland carcinogens, it is noted in the RoC. The RoC includes six substances noted to cause or possibly cause breast cancer in humans. These include DES, a synthetic form of estrogen that was used to prevent miscarriages; steroidal estrogens used for menopausal therapy; X- and gamma radiation; alcoholic beverages; tobacco smoking; and the sterilizing agent, ethylene oxide. The RoC also lists more than 60 substances that have been shown to cause mammary gland cancer in laboratory animals, including food additives or contaminants (e.g., byproducts from cooking meats at high temperatures); pharmaceuticals; consumer or manufacturing products (e.g., flame retardants, chemical solvents, dyes); industrial chemicals used to make rubber, vinyl and polyurethane foams; pesticides; and environmental pollutants formed largely from burning fuels. Most of these substances also caused tumors at many other tissue sites besides the mammary gland. In 2010, the NTP re-instituted experiments designed to expose the fetus and developing offspring, in addition to the adult, to chemicals of interest.[7, 8] This type of study design originally was used for several chemicals in the 1970s. These experiments will give new insights into the risks of early and later life chemical exposures on health outcomes in late life.

The National Toxicology Program, which issues the *Report on Carcinogens*, is incorporating early life exposures (*in utero* and postnatal) and additional mammary evaluations into carcinogenicity testing.

The NTP Office of Health Assessment and Translation (OHAT) is an environmental health resource for the public and regulatory and health agencies. This office conducts evaluations to assess the

- evidence that environmental chemicals, physical substances, or mixtures (collectively referred to as "substances") cause adverse health effects; it also provides opinions on whether these substances may be mammary gland carcinogens, based on knowledge about current human exposure levels. In addition, the OHAT organizes workshops or state-of-the-science evaluations to address issues of importance in environmental health sciences. OHAT assessments are published as NTP Monographs. Although the OHAT has not conducted any evaluations specifically related to breast cancer at this time, it has developed a process whereby the public may nominate substances of concern for consideration. Collaborators: the NIEHS, NCI, EPA, FDA, DoD, Consumer Product Safety Commission (CPSC), CDC/National Center for Environmental Health (NCEH), CDC/ATSDR, CDC/NIOSH, Occupational Safety and Health Administration (OSHA).

- **Agency for Toxic Substances and Disease Registry (ATSDR):** The ATSDR was created to perform public health assessments of waste sites, applied research in support of public health assessments, health surveillance through registries, information development and dissemination, and education and training concerning hazardous substances. The Agency also performs health consultations concerning specific hazardous substances and responds to emergency releases of hazardous substances. The ATSDR does not directly fund breast cancer research, but breast cancer risk often is addressed in its health assessments (e.g., the Camp Lejeune study mentioned in Section 7.2.3) and has been the focus of a number of consultations. Collaborators: The CDC, NIEHS, NTP, EPA.

- **Long Island Breast Cancer Study Project (LIBCSP):** Congress mandated this project in response to community concerns about possible environmental causes of the high breast cancer rates in Long Island counties (e.g., physical and chemical agents such as electromagnetic fields or organochlorines). The evidence from project studies did not support a relationship between the agents examined and the high breast cancer rates in the area. For example, no differences in organochlorine levels in blood were observed in women with and without breast cancer.[9] The study, however, only examined adult exposures/biomarkers and did not examine exposures in early life, which as noted in earlier chapters, is the period when environmental exposures are most likely to exert an effect on the breast. The studies also have yielded substantial evidence of lifestyle, reproductive, and genetic influences on breast cancer risk. In this study population, recreational physical activity was associated with a reduced risk of developing breast cancer[10] as well as lower mortality from breast cancer.[11] Collaborators: The NCI, NIEHS, State of New York.

- **Northeast and Mid-Atlantic Breast Cancer Study (NE/MA):** This congressionally mandated initiative included six studies that evaluated measurable environmental exposures associated with known risk factors that could contribute to the high rate of female breast cancer in the northeastern and mid-Atlantic regions of the United States. The findings provided a better understanding of genetic and lifestyle factors that may modify pre- and postmenopausal breast cancer risks from tobacco smoking, alcohol consumption, and exposure to polychlorinated biphenyls (PCBs) and the insecticide Mirex. Collaborators: The NCI and NIEHS.

7.3.2 Transdisciplinary Research

- **Breast Cancer and the Environment Research Centers (BCERC) Network:** The NIEHS and NCI established the BCERC program in 2003. This unique program functioned as a consortium of basic scientists, epidemiologists, community outreach experts, and community advocates within and across Centers. The program was created to conduct and integrate basic biologic, toxicologic, and epidemiologic research on normal mammary gland development as well as ways in which environmental exposures (chemicals, diet, and social factors) affect development over the life span. The project also translated findings into public health messages to educate young girls and women

- about breast cancer risk. The primary components of the Centers were: (1) laboratory-based research studies to compare the molecular changes that occur in normal breast development across the life span to changes that occur when environmental exposures are introduced; (2) a longitudinal epidemiologic study of the timing of female pubertal events, including the onset of breast development, age at menarche, and environmental and genetic factors that may affect pubertal maturation; and (3) Community Outreach and Translation Cores (COTCs) to integrate, translate, and disseminate scientific findings from all of the Centers. The BCERC program spanned 7 years (2003–2010). Hallmarks of this program were the partnerships created between scientists and advocates and the transdisciplinary discussion and integration of findings from laboratory-based and epidemiologic research to understand outcomes and seek explanations at the organ, cell, and molecular levels. Translation of the findings and engagement with many stakeholder communities also was a major component of BCERC from the outset. Important findings generated by the BCERCs included: (1) Peripubertal exposure to the chemical perfluorooctanoic acid (PFOA) altered the timing of mammary development in two strains of mice in a strain-dependent manner. The chemical caused endocrine disruption that altered the level of serum progesterone and growth factors required for normal mammary development;[12, 13] (2) BPA exposure in rats caused a heightened sensitivity to chemical carcinogens and protein changes consistent with altered sensitivity;[14] and (3) in African American but not White girls, the availability of neighborhood recreational facilities predicted delayed onset of puberty.[15] Collaborators: The NIEHS, NCI, AvonFW.

- **Breast Cancer and the Environment Research Program (BCERP):** The BCERP, which began in 2009, continues and extends the efforts of the BCERC to support transdisciplinary research on the interactions of environmental factors (including chemical, physical, and social environmental) with genetic factors throughout a woman's life span. The BCERP already has produced some important findings. For example, BCERP findings confirmed population-based estimates suggesting that girls are starting puberty earlier than in the past. At 7 years old, 10 percent of White girls, 23 percent of Black girls, 15 percent of Hispanic girls, and 2 percent of Asian girls in the study had started breast development.[16] BCERP studies also demonstrated that phthalates and phytoestrogens act as weak estrogens and have small associations with pubertal timing.[17] Collaborators: The NIEHS, NCI, AvonFW, CDC, Susan G. Komen for the Cure, and a number of breast cancer coalitions and foundations.

- **NIH Obesity Research Task Force:** This Task Force was established to accelerate progress in obesity research across the NIH. It involves multiple NIH Institutes and Centers in developing approaches to accelerate research on the biological and social mechanisms that underlie obesity; the health consequences of obesity, including obesity-related cancers such as breast cancer; and interventions to prevent obesity and facilitate weight loss. In its strategic plan, the Task Force calls for research to examine how environmental toxicants and other chemical exposures affect the development of obesity in children and adults.[18] Collaborators: multiple Institutes and Centers of the NIH.

7.3.3 Epidemiology

- **Sister Study:** The Sister Study is a long-term, national study of the ways in which the environment and genes affect women's chances of developing breast cancer when they have no personal history of cancer but have a biological (full or half) sister who was diagnosed with the disease.[19,20] The study, which recruited participants from August 2003 through July 2009, enrolled more than 50,000 women ages 35–74. Participants were recruited from across the United States and Puerto Rico, with special attention paid to recruiting a diverse cohort in terms of race/ethnicity, geographic location, and exposures. Nearly all participants provided blood, urine, toenail, and house dust samples at baseline that were stored in

- a biorepository. Unlike previous cohort studies that focused on exogenous hormones, diet, and lifestyle, the Sister Study is collecting extensive information on occupational and environmental exposures throughout the life course, especially during vulnerable time periods such as *in utero*, around puberty, and prior to a first full-term pregnancy. Geocoding of current and past residences allows for linkage to various geographically based datasets to further characterize participants' lifetime environmental exposures. This study identified maternal factors as well as factors related to birth and *in utero* exposures that appeared to affect the timing of a woman's menopause later in life.[21] The study also found that, in spite of having a family history of breast cancer, most women in this study did not adhere to ACS guidelines for diet, physical activity, and body mass.[22] Collaborators: The NIEHS, National Institute on Minority Health and Health Disparities (NIMHD), ACS, Susan G. Komen for the Cure, Intercultural Cancer Council, Sisters Network, Inc., Breast Cancer Network of Strength.

- **Two Sister Study:** A related study, the Two Sister Study, collected information similar to that collected by the Sister Study from approximately 1,600 women with breast cancer diagnosed before the age of 50 whose sister(s) were enrolled in the Sister Study. The Two Sister Study collected DNA from living parents for family-based studies of genetic and environmental factors that increase a woman's risk for young onset breast cancer. A new partnership with the CDC is taking advantage of this study to examine social factors and quality of life in breast cancer survivors. In addition, collaboration with an extramural investigator (at the University of Washington) is enabling study of the influence of air pollution on a range of health outcomes, including breast cancer. Other ongoing and future collaborations involve laboratory-based studies of genetic influences and potential biomarkers of breast cancer risk or prognosis. Collaborators: The CDC, NIEHS, Susan G. Komen for the Cure.

- **Agricultural Health Study:** The Agricultural Health Study is a prospective, longitudinal investigation of the effects of environmental, occupational, dietary, and genetic factors on the health of agricultural workers and their spouses.[23, 24] An early study report found little consistent evidence of risk for breast cancer associated with pesticides. The study found that farmers' wives who reported applying pesticides had a lower breast cancer risk than wives not reporting applying pesticides, possibly due to a protective effect of working on a farm. The study did, however, find evidence of risk associated with specific pesticides and farm characteristics.[25] Collaborators: The NCI, NIEHS, EPA, NIOSH.

- **Children's Environmental Health and Disease Prevention Centers (CEHC):** CEHC supports greater understanding of the linkage between *in utero* exposures and adverse health outcomes in later life, including childhood leukemia and pubertal timing and progression. Although these cohort studies are not designed to evaluate breast cancer risk directly, they shed light on exposures that may contribute to risk factors for developing breast cancer. Collaborators: The NIEHS, EPA/National Center for Environmental Research (NCER).

7.3.4 Other Major Research Programs

- **Tox21:** Tox21 is a multi-agency research program designed to identify patterns of biological responses induced by chemical compounds to characterize toxicity/disease pathways, facilitate the extrapolation of animal research findings to humans, prioritize compounds for more extensive toxicologic evaluation, and develop predictive models of biologic response in humans. Ultimately, Tox21 is expected to develop strategies that can be used by regulatory agencies to regulate chemicals and reduce the current reliance on animal testing for toxicologic assessments. The current Tox21 10,000-compound library being screened for activity in different nuclear receptor and stress response pathway assays includes a number of substances known or suspected to induce breast cancer in animal models and/or humans. The program accepts nominations for biochemical and cell-based assays that could be used in a high-throughput screening

- facility, including those based on cells derived from normal breast tissue. Collaborators: The NTP/NIEHS, NIH Chemical Genomics Center (NCGC)/NCATS, FDA, EPA/NCCT.

- **High-Throughput Risk Assessment (HTRA) Project:** Part of the Tox21 project, the HTRA project (Figure 7.6) is studying new and integrative approaches to calculating exposure limits for environmental substances that will protect public health. The assessment model starts with identification of the biologic pathways that are adversely affected by exposures, incorporates available *in vitro* measurements (e.g., via the ToxCast/Tox21 programs), proceeds to estimation of *in vivo* biologic pathway altering doses (BPAD) via pharmacokinetics and pharmacodynamics modeling, and ends by incorporating uncertainty and population variability in the model. A key aspect of this model is the use of reverse toxicokinetics and the combination of experimental data with pharmacokinetics modeling to estimate dose-to-concentration scaling.[26-28] Collaborators: The NTP/NIEHS, NIH NCGC/NCATS, EPA.

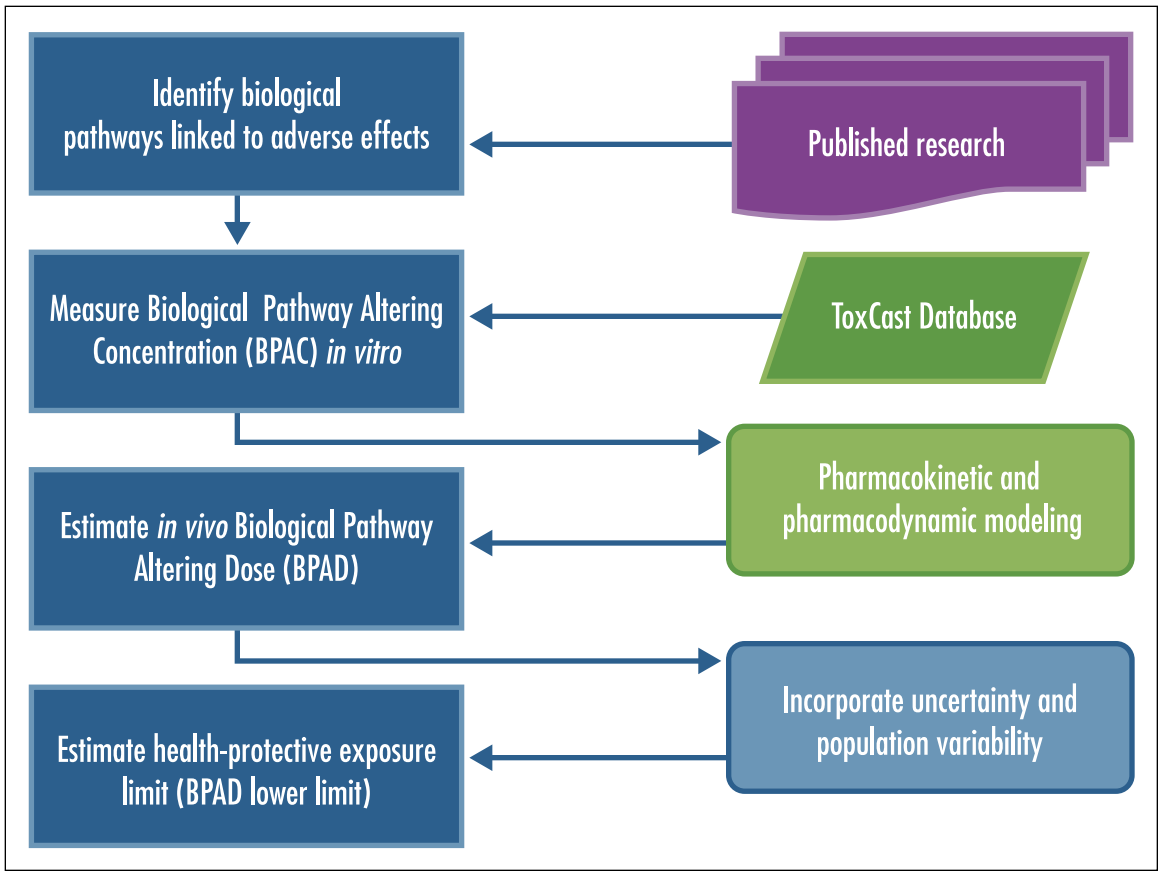
- **Building on National Initiatives for New Chemicals Screening:** This research program at the University of California utilizes data from EPA's ToxCast program (see Section 7.2.4) and the Tox21 program to prioritize chemicals for further evaluation and regulation. The research team is selecting validated tests from ToxCast and translating them to a variety of breast cell models. Assays are being run for 60 substances, comparing those that are not associated with breast cancer to those known to be breast carcinogens to identify assays most likely to predict substances that will cause mammary gland tumors in animals. Collaborators: The EPA, NTP, University of California at Berkeley.

- **Making Chemicals Testing Relevant to Breast Cancer:** This research program is aimed at transferring EPA's ToxCast assays into mammary cell lines, testing an extended set of chemicals (e.g., potential rodent mammary gland carcinogens), evaluating how well the assays discriminate between the potential mammary carcinogens and noncarcinogens, and determining whether the assays in mammary cell lines improve this prediction. Collaborators: The EPA, CBCRP, and Silent Spring Institute.

- **The Breast Cancer and Chemicals Policy Project (BCCP):** Supported by a grant from the CBCRP, this project aims to close the data gap in chemical hazard information by proposing an approach to chemical testing that accounts for the events in biologic pathways associated with increased risk of breast cancer. In 2010, a panel of 20 scientists and policy experts convened to review the biological mechanisms associated with breast cancer and propose a strategy for screening and identifying chemicals that could increase the risk of the disease. The panel followed a unique "disease end point" model, working backward from a disease to identify the changes caused by chemicals that could serve as early indicators of toxicity. Although this approach was recommended by the National Academy of Sciences in its report *Toxicity Testing in the 21st Century*, this is the first time it has been implemented for any disease, including breast cancer. Collaborators: The CBCRP, Natural Resources Defense Council, University of California at Berkeley.

- **The Adverse Outcome Pathway (AOP) Model:** EPA's Office of Research and Development and its Office of Chemical Safety and Pollution Prevention (OCSPP) currently are utilizing the AOP model as a tool for linking the specific harmful effects of an environmental exposure to a set of direct initiating events at the molecular level. In the AOP model, events at the molecular level that have been associated with a chemical exposure are linked to adverse outcomes in an individual or a population. Key organs respond to these cellular changes that, over time, result in alterations of tissue physiology, function, and development. These changes eventually lead to cancer, impaired development or reproduction, and death. If exposure is sufficiently high and widespread, it is possible to find associations between exposure and adverse outcomes

Figure 7.6. Outline of the Tox21 program high-throughput risk assessment (HTRA) model



The HTRA approach is a five-step process that calculates BPAD, which is useful in estimating acceptable exposure levels. This process is described in detail in an article published in EPA's *science in ACTION* newsletter.[29] The conceptual approach needs further development and testing before being used in the field. Adapted from Figure 1 in "Estimating Toxicity-Related Biological Pathway Alternating Doses for High-Throughput Chemical Risk Assessment" published in EPA *science in ACTION* (http://www.epa.gov/ncct/download_files/factsheets/High-Throughput%20Chemical%20Risk%20Assessment_Fact_Sheet_2-13-2011.pdf).

- at the population level. The EPA is exploring the application of this new approach in support of scientifically rigorous risk assessment activities. Collaborators: The EPA, U.S. Army Corps of Engineers Engineer Research and Development Center.

7.3.5 Summary: Collaborative Projects on Breast Cancer and the Environment

The Committee identified several collaborative projects relevant to breast cancer and the environment. Many of these collaborations have generated findings important to advancing knowledge about this field. The NCI and NIEHS have initiated a number of collaborations focused on physical and chemical environmental exposures and breast cancer risk. Some were congressionally mandated and others were initiated by the Institutes to support transdisciplinary projects that brought together basic and population scientists with advocates and community members. The NIEHS and EPA have numerous collaborations related to toxicologic studies associated with breast cancer. The NTP, which evaluates the carcinogenicity of chemical and physical agents for breast and other cancers, also collaborates extensively with a number of health and environment-oriented agencies. One notable public-private partnership is the BCERP; although principally supported by the NCI and NEIHS, the Susan G. Komen for the Cure Foundation and AvonFW also have contributed to the research effort.

7.4 Promoting Innovation

The majority of federal breast cancer research programs fund investigator initiated research projects under the belief that the most important scientific breakthroughs come from unexpected areas of inquiry suggested by the scientists themselves.

We must foster a scientific research environment that promotes "out of the box" thinking and innovation.

Although the extent of innovation is an important evaluation criterion for most grant mechanisms, a number of funders have developed special programs intended to support research that is highly innovative, very creative, and potentially transformative in an area of science. These types of programs, although not specific to breast cancer research, may be of value in supporting researchers and ideas that will unravel the complexities of the relationship between environmental factors and breast cancer. To date, these programs have not been used to any great extent to support studies of breast cancer and the environment. These programs have the potential, however, to support promising high-impact research in this area. Examples of such programs include:

- **NIH Common Fund:** Enacted into law by Congress through the 2006 NIH Reform Act, this fund was created to support crosscutting, trans-NIH programs that require participation by at least two NIH ICs on complex problems in biomedical sciences. Initiatives that comprise Common Fund programs provide limited term investments in strategic areas to stimulate further research. The intent of these programs is to provide a strategic and nimble mechanism for removing roadblocks that impede basic scientific discovery and its translation into improved human health. These programs capitalize on emerging opportunities to catalyze the rate of progress across multiple fields. Common Fund programs are expected to transform the manner in which a broad spectrum of health research is conducted. Several types of Common Programs exist, including the high-risk/high-impact programs that solicit highly innovative proposals and award substantial funds for research with potential impact beyond that of a traditional grant. These include programs for investigators across the career spectrum.

- **NIH Director's Transformative Research Awards:** This program seeks grant proposals from institutions/organizations for groundbreaking, innovative, high-risk, and/or unconventional research with the potential to create new scientific paradigms or challenge existing ones. Projects must clearly demonstrate the potential to produce a major impact in a broad area of biomedical or behavioral research. These grants are designed to support team science that brings together a diverse set of disciplines to tackle complex problems.

- **NIH Director's Pioneer Awards:** These awards are designed to support individual scientists who propose pioneering and possibly transforming approaches to major challenges in biomedical and behavioral research. To be considered pioneering, the proposed research must reflect ideas that are substantially different from those already being pursued in the investigator's laboratory or elsewhere.

- **NIH Director's New Innovator Awards:** Many new investigators have exceptionally innovative research ideas, but not the preliminary data required to fare well in the traditional NIH peer review system. As part of NIH's commitment to increasing opportunities for new scientists, it has created this program to support exceptionally creative new investigators who propose highly innovative projects that have the potential for unusually high impact. This award complements ongoing efforts by the NIH and its ICs to fund new investigators through regular grants and other mechanisms.

- **NIEHS Outstanding New Environmental Scientist (ONES) Awards:** These awards are designed to identify and attract outstanding new environmental health researchers and encourage their early transition to independence. This program targets

- exceptionally talented new investigators who intend to make a long-term career commitment to research in the mission areas of the NIEHS. The award assists them in launching an innovative research program focusing on problems of environmental exposures and human biology, pathophysiology, and disease.

- **DoD Idea and Concept Awards:** Since its inception in 1992, the DoD BCRP has developed mechanisms designed to fuel the pipeline of innovative, high-risk/high-reward research ideas. The BCRP Idea Award, first offered in 1993, was developed to support early-stage ideas with little or no preliminary data that could introduce new paradigms or challenge existing ones. At that time, such high-risk but potentially high-gain research opportunities were significantly underfunded by traditional funding mechanisms. In 1999, the BCRP created the Concept Award to support the exploration of highly innovative, untested concepts to reveal entirely new avenues of investigation. Preliminary data is not allowed in a Concept Award, and a blinded peer review ensures that the focus is on the most innovative, early ideas rather than the reputation of the investigators and their institutions. Another approach to supporting innovation was the creation of the Innovator Award in 2001 to support visionary individuals who have demonstrated creativity, innovative work, and leadership in any field and have high potential for groundbreaking achievements in breast cancer. Collectively, innovation-focused awards have represented a major proportion (63.3%) of the BCRP portfolio (FY 2006–FY 2010).

- **DoD Era of Hope Scholar Awards:** This program supports exceptionally talented, early-career investigators who are identified as having high potential for innovation in breast cancer research. Successful candidates have demonstrated that they are the "best and brightest" in their field(s) through extraordinary creativity, vision, and productivity. They exhibit strong potential for leadership in the breast cancer research community and are able to articulate a vision for the eradication of breast cancer. These individuals challenge current dogma and demonstrate an ability to look beyond tradition and convention.

- **America COMPETES Act:** COMPETES gives every department and agency the authority to conduct prize competitions for innovations in areas called for in President Obama's 2009 Strategy for American Innovation. This report called for innovations in health care technology that would help prevent medical errors, improve health care quality, reduce costs, and cement U.S. leadership of this emerging industry. Perhaps of more importance to the study of breast cancer and the environment, the report also called for scientific innovations to address the "grand challenges" of the 21st century, such as the elimination of cancer. The challenge.gov website describes all of the "challenges" initiated by government agencies in pursuit of creative ideas and solutions. The NCI, for example, recently provided multiple awards for innovative software applications (apps) that use public data and address challenges faced by consumers, clinicians, or researchers at one or more points on the cancer control continuum, including prevention.

Federal initiatives to support exceptionally innovative research account for a small percentage of the agencies' grant portfolios. Typically, these initiatives cover almost any area of scientific research related to health.

Nongovernmental agencies also have been experimenting with funding mechanisms to support greater research innovation. Examples include:

- **Howard Hughes Medical Institute (HHMI):** The HHMI supports a philosophy to "fund the people, not the projects." Research conducted by HHMI investigators is not limited to a rigid set of aims, which allows investigators to more easily pursue new research leads.

- **European Research Council (ERC):** The ERC has a grant program to support the pursuit of questions at or beyond the frontiers of knowledge, without

- regard for established disciplinary boundaries. The program encourages transdisciplinary research; research in emerging fields; and unconventional, innovative approaches and scientific inventions when the expected impact could be significant.

7.5 Increasing Diversity of the Research Workforce

A diverse research workforce is essential for the nation's success (NAS, 2011). NIH Director Francis Collins and Deputy Director Lawrence Tabak noted that the "NIH mission can only be achieved if the best and brightest biomedical researchers, regardless of race, ethnicity, disability, socioeconomic background, or gender, are recruited and retained in our workforce."[30] Unfortunately, minority populations continue to be underrepresented in the sciences, technology, and engineering professions and, more specifically, among research scientists.[31] A recent report found that African American researchers are 10 percent less likely to receive NIH investigator-initiated (R01) grant funding than Whites, even when other factors such as training and previous awards are taken into account.[32]

The NIH has long supported programs for institutions and individuals to increase the diversity of the scientific workforce. The Committee identified a number of NIH initiatives designed to involve minority researchers and institutions in research activities, attract racial/ethnic minorities to a career in scientific research, and assist them in the development of those careers. For example, NIH's NIMHD funds several programs that promote involvement of minority individuals in scientific research, including two programs focused on training and biomedical sciences research. None of these programs is breast cancer specific.

- **Research Endowment Program:** This congressionally mandated initiative promotes minority health and health disparities research capacity building at eligible academic institutions by investing in the education and training of underrepresented minorities and socioeconomically disadvantaged individuals.
- **Research Centers in Minority Institutions (RCMI) Program:** This program develops and strengthens the research infrastructure of minority institutions by expanding human and physical resources for conducting basic, clinical, and translational research. It provides grants to institutions that award doctoral degrees in the health professions or health-related sciences and have a significant enrollment of students from racial and ethnic minority groups that are underrepresented in the biomedical sciences.
- **NIH Diversity Supplement Program:** These supplements provide additional support that allows principal investigators to improve the diversity of the research workforce by supporting and recruiting students, postdoctorates, and eligible investigators from groups that have been shown to be underrepresented in health-related research; or to accommodate a disability so that the disabled individual can continue to work on the research project.
- **Ruth L. Kirschstein National Research Service Award (NRSA):** These Institutional Research Training Grants are awarded to eligible individuals to support predoctoral and postdoctoral research training to help ensure that a diverse and highly trained workforce is available to assume leadership roles related to the nation's biomedical, behavioral, and clinical research agenda.

The NIH Director's Working Group on Diversity in Biomedical Research Workforce is exploring what it will take to create a sustainable research environment that supports diversity.[33] The NIH also is interested in investigating the causes of the differential success rates in proposal funding between researchers of different racial ethnic groups and in developing ways to eliminate this disparity. One effort, the Early Career Reviewer (ECR) program, is designed to involve more minority junior researchers in research peer-review panels. Not only does this increase the diversity of review panels, it also exposes these new researchers to what it takes to create a fundable research proposal and provides opportunities for professional networking.

Finding ways to improve diversity in the biomedical research workforce will be important to ensuring the success of the entire research enterprise. In particular, a diverse research workforce will be needed to meet the challenges of studying breast cancer and the environment.

7.6 Research to Accelerate Translation

Rapid translation of research results into effective action is necessary to reduce the burden of breast cancer. Although a plan for the translation of research findings is an important evaluation criterion for many grant mechanisms, many investigators have limited knowledge about the most effective approaches for translating research findings into action. In response to this need, many agencies have begun to support implementation science research. Implementation science research "emphasizes investigation and understanding of the processes involved in the adoption, implementation, and sustainability of research."[34] NIH has developed funding initiatives to support this type of research. These include:

- **NIH's Fogarty International Center:** This Center supports and facilitates global health research conducted by U.S. and international investigators, is fostering research to examine the process of transferring effective interventions into local settings. The Center recognizes that these local settings may have some differences from the ones in which the intervention was developed and tested and what worked in one may not work in another. Funding opportunity announcements (for example, http://grants.nih.gov/grants/guide/pa-files/PAR-10-038.html) are intended to encourage transdisciplinary teams of scientists and practice stakeholders to work together to (1) develop and/or test conceptual models of dissemination and implementation that may be applied across diverse community and practice settings, and (2) design studies that will accurately assess the outcomes of dissemination and implementation efforts.
- **Training Institute for Dissemination and Implementation Research in Health:** Multiple NIH ICs and the U.S. Department of Veterans Affairs have sponsored this annual Training Institute to train researchers how to conduct dissemination and implementation research in health. Trainees are expected not only to complete the training, but to commit to being prepared to share what they have learned at the Institute to help advance the field of dissemination and implementation research.

7.7 Research Advocacy and Stakeholder Involvement in Research

Advocates and community organizations have long played a direct role in establishing priorities and securing funding for breast cancer research, as noted in Chapter 4. Similarly, advocates and community organizations play a crucial role in disseminating information to patients and the general population

Advocates have called for and secured increased funding for breast cancer research and the inclusion of breast cancer survivors and community stakeholders in the research process.

and in the recruitment and retention of study participants. This latter role is discussed in more detail in Chapter 8. This section describes how advocates and the public are involved in federally funded research on breast cancer and the environment.

At a program development level, advocates and public members of agency advisory committees have pushed agencies to support research that includes community members as partners with scientists. This type of contribution is shown in the upper third of Figure 7.7. Examples include the development of the Partnerships for Environmental Public Health (PEPH) program, which emphasizes community engagement across the NIEHS research portfolio and community-based participatory research (CBPR) studies to address compelling public health problems

in communities. CBPR research is an applied collaborative approach that enables community residents to more actively participate in the full spectrum of research (from conception→design→conduct→ analysis→interpretation→conclusions→ communication of results), with a goal of influencing change in community health, systems, programs, or policies.[35] The NIMHD, NIEHS, NIH/Office of Behavioral and Social Sciences Research (OBSSR), NCI, and EPA have embraced this approach and regularly collaborate on the implementation of programs that use it. As a result, some CBPR research grants have been funded in recent years that focus on disparities in breast cancer and breast cancer and the environment (see Chapter 8).

For some programs, such as BCERP (described in Section 7.3.2), investigators work closely with community members and advocates to develop, refine, and disseminate specific projects. This includes providing input at the research program design stage and participating in scientific peer review and agency programmatic review efforts (middle third of Figure 7.7), and support of research results dissemination efforts (bottom third of Figure 7.7). This level of community participation, however, occurs in a small minority of supported programs. The Committee saw opportunities to expand and improve this model, which has been shown to be particularly effective in conducting research in underrepresented minority populations.[36-38] A community-based approach could be applied to studies in communities in which exposures to environmental hazards are high to improve understanding of the causes of breast cancer, barriers to conducting research (e.g., health literacy), and the most effective approaches to developing and implementing interventions to reduce exposures and disease risk.

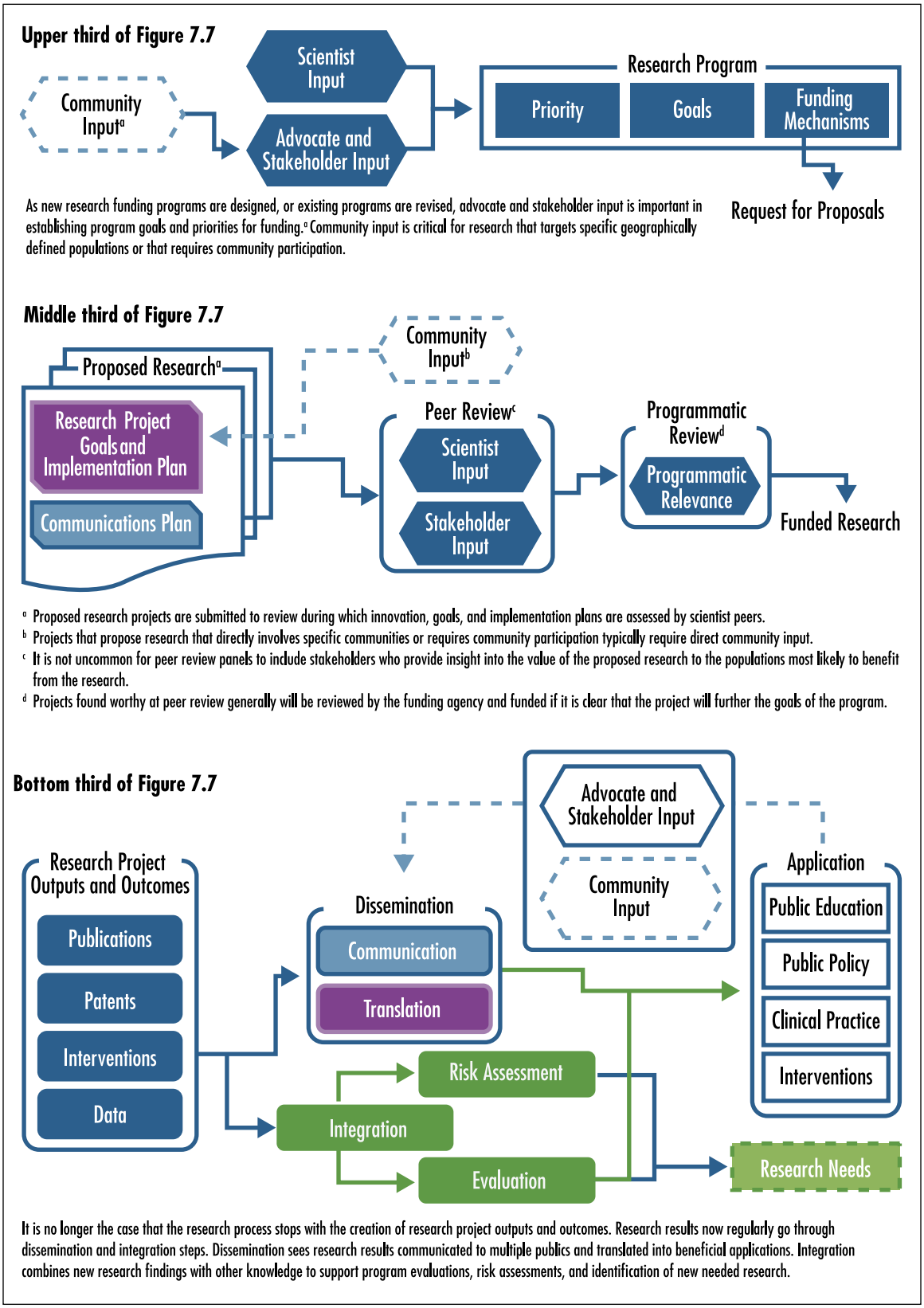
In addition to participating in the actual research, advocates and community members are involved in evaluating grants and on advisory committees to the Directors of federal agencies. The two-stage proposal review process used by many federal agencies includes peer review at the first stage and programmatic review at the second stage (middle third of Figure 7.7). At peer review, scientists provide input on the scientific merit of proposals, with stakeholders providing input as to whether proposed research will raise concerns with the public or address public priorities. All DoD and CBCRP first-stage review panels, for example, include advocates and community representatives. Funding announcements on breast cancer and the environment that are developed and reviewed by the NIEHS include community representatives at the first stage of review. The NCI sometimes uses consumer advocates in peer review through its Consumer Advocates in Research and Related Activities (CARRA) program. In addition, many NGO peer review processes utilize stakeholders as voting members of research peer-review panels.[39, 40]

In the second stage of proposal review, scientifically acceptable proposals are evaluated for the extent to which they address the priority goals of the research program. Advocate input at this point can help to identify the research proposals that hold the greatest potential to affect their communities. Many federal advisory committees that provide guidance to the leadership of the organization on a wide range of research and policy matters now include voting public representatives. Some of these advisory committees also are responsible for the second level of grant application review.

Examples of advocate and stakeholder involvement in research policy and decision making include:

- **Department of Defense:** The role of advocates or consumer representatives in the creation of the DoD BCRP resulted in a level of involvement that was unprecedented in other research funding organizations. Consumer representatives are fully integrated as voting members at all levels of program development, vision setting, and proposal review, and some of the BCRP funding mechanisms require advocates on the research team.[41] The BCRP currently utilizes consumer representatives in addition to scientists and clinicians on its peer review panels and as members of its BCRP Integration Panel. On peer review panels (first-stage review), consumer representatives read and

Figure 7.7. Two-stage research review and dissemination process demonstrating advocate, stakeholder, and community input in program and project review



- evaluate research study applications for merit and the potential impact of breast cancer and actively participate in peer review panel discussions. The Integration Panel (second-stage review) consumer representatives make final funding recommendations that determine the overall research portfolio. In addition, the Integration Panel sets the program's vision and makes recommendations on its investment strategy every year.

- **Advisory Committee on Breast Cancer in Young Women (ACBCYW):** This committee was created to advise the CDC Director (at program design) on formative research, development, implementation, and evaluation of evidence-based approaches to advance understanding and awareness of breast cancer among young women through prevention research, public and health professional education and awareness activities, and emerging prevention strategies. The committee includes organizational representatives and individuals with expertise in breast cancer, disease prevention, early detection, diagnosis, public health, social marketing, genetic screening and counseling, treatment, rehabilitation, palliative care, and survivorship in young women, or in related disciplines with a specific focus on young women.

- **NIH Institutes' and Centers' Councils:** The NIH has long involved community members in the research process through representation on NIH Councils. NIH Councils are committees formed by each IC to provide advice to the Institute Directors on matters related to research and organizational directions and to provide second-level review of research proposed for funding. At any given time, most ICs have one or more community representatives on their Councils. One-third of the nongovernmental members of NIEHS' council come from the public.

- **The NIH Director's Council of Public Representatives (COPR):** This Council is made up of members of the public who advise the NIH Director on issues related to public participation in NIH activities, outreach efforts, and other matters of public interest, including establishment of research funding priorities.

- **NCI Director's Consumer Liaison Group (DCLG):** These advisory committees are composed of advocate leaders who provide input into current and future NCI research programs. The DCLG also includes cancer patients and recent cancer survivors to provide insight on the non-scientific challenges to research, including how research goals, patient needs, health policy, and advocacy issues affect agency research programs. With the best interests of the cancer patient in mind, the DCLG reviews and makes recommendations to the NCI Director on new research approaches, ways to promote innovation, identify and overcome risks and barriers, and the many other issues and challenges faced by the NCI as it strives to achieve its stated research goals.

- **NCI Office of Advocacy Relations Consumer Advocates in Research and Related Activities (CARRA) Program:** Consisting of NCI staff and representatives from advocacy groups, participants in this program provide input on NCI activities that involve scientific research and communication of findings and foster an organizational atmosphere that values the contributions of consumer advocates.

There are many examples of the successful involvement of advocates and community representatives in the breast cancer and the environment research enterprise, including in the (1) development, design, and execution of research projects; (2) peer and programmatic review; and (3) agency oversight of research. The extent and types of this involvement, however, vary widely. Some agencies have very limited involvement of advocates and community members, and most research on breast cancer and the environment still does not include any advocate involvement.

7.8 Gaps and Recommendations

The Committee reviewed the current state of the federal breast cancer and the environment research portfolio and concluded that the proportion of current funding that focuses on prevention or etiologic research is disproportionately small. The Committee recommends a shift in the portfolio toward prevention science to advance understanding of the complex causal web of the disease. Transdisciplinary methods and approaches that involve both scientists and advocates will be necessary to study the contributions of the environment in both causing and preventing this complex disease. Breast cancer survivors and advocates bring a unique perspective and should have increased input into programmatic priority-setting and project review.

Chapter 6 identified a number of knowledge gaps and made recommendations about specific areas of science that needed to be pursued to advance and accelerate our understanding of breast cancer and the environment. What is clear from the recommendations in Chapter 6 is that breast cancer encompasses many diseases that may have several distinct causes, are hard to measure, and may operate over a lifetime. The underlying biological mechanisms of breast cancer are very complicated and require substantial research to fully unravel them. The Committee identified a number of needs and ways to improve how agencies support science on breast cancer and the environment that would help to fill the research gaps identified in Chapter 6. The Committee expects that these recommendations will accelerate the science, and that the results of this science will be used to prevent breast cancer.

Gap: Supporting increased transdisciplinary research

The Committee found multiple examples of federal agency collaboration in breast cancer and the environment research. The transdisciplinary focus of these collaborations, however, could be strengthened.

Specifically, the Committee sees the need for modifications to training programs and funding mechanisms to better support transdisciplinary research. In particular, the Committee identified a need for more scientists to be exposed to transdisciplinary research and to develop skill sets that will enable them to function in transdisciplinary research environments. Currently, opportunities to develop these skills are limited. Scientists at all levels—from students through mid- and later career stages—would benefit from training in how to function well in transdisciplinary settings.

> Prevention research must become a priority across the federal government. Breast cancer prevention research makes up only a small portion of current research funding.

All funders currently work to match expertise on peer review panels to the scientific content in the group of applications that they are reviewing. This approach, however, does not always result in reviewers with specific expertise on breast cancer and environmental issues relevant to the application. When considering transdisciplinary applications in this field, the review panel must include a wider diversity of disciplines than might be needed for single laboratory applications.

Recommendation: Increase support for successful transdisciplinary research projects, and encourage the formation of more transdisciplinary partnerships to address knowledge gaps and integrate current understanding of breast cancer and the environment.

New models for transdisciplinary research continue to be developed, implemented, and expanded and will be needed to create solutions to the challenging problems that are bottlenecks to progress. Mechanisms are needed for investing in short-term collaborations that draw specific expertise from multiple disciplines to conduct high-risk, high-return research that presently does not receive high priority in existing programs. This includes support for: (1) innovative "outside the box" ideas, (2) follow up on unanticipated

discoveries, (3) development of needed tools and models requiring expertise from multiple disciplines, and (4) validation of key findings not adequately replicated in the original research.

Agencies must do more to support the creation of a breast cancer research workforce that can work effectively in the multidisciplinary teams to understand the full complexity of breast cancer and the environment interactions and make progress toward filling knowledge gaps. Examples of training that can enable scientists to function in transdisciplinary settings already exist. One excellent program developed by NIH's OBSSR provides training in team science.[42] Another unique example is the Columbia University Mailman School of Public Health curriculum for its Masters of Public Health Program. Introduced in 2012, this program focuses on the skill sets needed for complex public health challenges and could be a model for other programs that train students to work in a transdisciplinary way. The curriculum groups students from different disciplines to work jointly on crosscutting, case-based learning activities and includes a course on leadership and innovation skill development.[43]

Programs that enable scientists to work in different disciplinary settings or on teams that already have adopted a transdisciplinary approach also are valuable. Short-term appointments by academic and federal scientists at other U.S. federal agencies such as the EPA, FDA, ATSDR, CDC, NIH laboratories or intramural research groups, or academic centers, may provide unique opportunities for training in state-of-the-art scientific methods and technologies outside of a scientist's field of expertise. Training or short-term appointments by scientists in offices of communication, public engagement, policy, and planning also are valuable to increase knowledge about the translation and dissemination of research.

Persons organizing review panels should strive to include representation from many disciplines on panels that review applications on breast cancer and the environment hypotheses that involve transdisciplinary approaches. A multidisciplinary review panel is likely to provide a more thorough and nuanced discussion of the quality and appropriateness of hypotheses and methods proposed to solve the complex questions that arise in the study of breast cancer and the environment.

Gap: Involving a diverse population of scientists in research on environmental causes of breast cancer

The Committee recognizes that federal agencies already are working to increase minority representation in the biomedical research community. Federal programs, however, need to expand efforts to support and train a diverse population of scientists in breast cancer and the environment research, especially scientists from minority communities.

Recommendation: Develop a more diverse community of scientists working on breast cancer and the environment.

Federal agencies and nongovernmental entities involved in health research must create more programs to provide the financial, mentoring, and other support needed by many minority students and new investigators to develop careers and become independent, successful investigators who can pursue scientific complexities such as the role of the environment in breast cancer. Career development programs are needed for these scientists to: (1) support expansion of their research capabilities, (2) teach them to work in and lead transdisciplinary teams, and (3) move their research findings into the clinic or communities of need.

Gap: Using comprehensive electronic information on funded health research

The portfolio analysis found no studies that were duplicated across the agencies examined. This finding was encouraging, considering the efforts of both the NIH and DoD to avoid duplication. These efforts

include, but are not limited to, searching agency databases for funded awards. The agencies' different data systems, however, make it challenging to compare portfolios and identify and verify duplication of research projects. All NIH and other breast cancer funding agencies primarily utilize their own grants databases, which are not compatible with each other.

> The Committee supports the GAO recommendation that "the Director of NIH as well as the Secretaries of DoD and VA should determine ways to improve access to comprehensive electronic information on funded health research shared among agency officials and improve the ability of agency officials to identify possible duplication."

Although the ICRP database contains research portfolio data for the NCI, DoD, and several NGOs, it does not include data for all NIH Institutes and other federal agencies. This situation limits the ability to identify potential duplication and overlap of research studies.

Coding of externally funded research using the CSO system helped in the review of NCI, DoD, and NGO projects, but molecular and cellular discovery research performed at other NIH Institutes, the EPA and FDA, and cancer control and prevention projects at the CDC were not coded. In addition, much intramural research was not coded to the CSO, requiring the Committee to manually review and code this research for this report.

Recommendation: Support the U.S. Government Accountability Office (GAO) recommendation on improving access to comprehensive electronic information on funded health research.

The Committee supports a recent GAO report that noted the challenges of identifying potential overlap and duplication when it examined current approaches to coordinating funding of breast cancer and posttraumatic stress disorder research by the NIH, DoD, and VA. Based on findings, the GAO concluded that "the Director of NIH as well as the Secretaries of DoD and VA should determine ways to improve access to comprehensive electronic information on funded health research shared among agency officials and improve the ability of agency officials to identify possible duplication."[44] NIH's RePORT system could be one of the systems examined to address this recommendation.

The Committee further recommends developing improved systems to monitor research on breast cancer and the environment across agencies and NGOs. To facilitate this type of monitoring and analysis of portfolios across agencies, the IBCERCC encourages an expansion of CSO coding to all federal agency regulatory, health, and medical research at all NIH Institutes and other relevant funding agencies. Future coding should incorporate more categories in the outline, allowing researchers to specify in greater detail the research topic being funded and its relevance to cancer (as well as other chronic disease conditions).

Gap: Coordination across agencies with clear strategic goals

The Committee identified many federal agencies and NGOs that fund breast cancer and the environment research or are responsible for developing public health interventions and assessments for environmental regulation. When viewed through the breast cancer research lens, it is clear that there is no one group or agency that is ultimately responsible for the overall efforts relevant to breast cancer and the environment, which consists of a complex set of research and translation programs. No federal process, however, supports coordinated strategic planning across agencies for funding projects related to breast cancer and the environment. The Committee identified three specific needs in this area: (1) the need for additional coordination of research activities relevant to breast cancer and the environment, (2) the need for a mechanism for monitoring progress in this field of study, (3) the need for a forum to develop and support strategic goals for breast cancer and the environment research funding.

Recommendation: Create a mechanism to facilitate joint strategic planning and coordination among funders of research on breast cancer and the environment, with breast cancer prevention as the goal.

Joint strategic planning and better coordination of the efforts of both governmental and nongovernmental funders would increase the visibility of research on breast cancer and the environment, promote the goal of breast cancer prevention, facilitate sharing of resources, help identify the most critical scientific questions, and monitor progress toward answering those questions. One model of joint strategic planning and coordination is the National Collaborative on Childhood Obesity Research, whose members include the CDC, NIH, U.S. Department of Agriculture, and the Robert Wood Johnson Foundation. The mission of this funders' forum is to reduce obesity in the United States by maximizing outcomes from research, building the capacity for research and surveillance, creating and supporting the mechanisms and infrastructure needed for research translation and dissemination, and supporting evaluations. Similar forums focusing on breast cancer and the environment research could be formed to include representatives from federal and nongovernmental funding organizations, with additional members representing academia, advocates, communities, policy makers, public health and clinical practitioners, and other stakeholders.

Gap: Development of knowledge integration tools

Chapters 5 and 6 established that: (1) a large number of genetic and environmental factors may contribute to breast cancer, (2) relating findings in animal studies to humans requires an understanding of the many nuances of interspecies differences and similarities, and (3) many processes and steps are needed to establish that an environmental factor is causally related to breast cancer. There is a need for tools, databases, or flow charts that can be referred to as "frameworks" to help in understanding and organizing the complex factors, relationships, and processes involved in the study of breast cancer and the environment. The knowledge integration tools must consider not only the scientific data, but also what studies are being conducted and what progress is being made so that gaps can be identified easily. These tools must support the development and implementation of a strategic plan for breast cancer prevention and facilitate the monitoring of progress in achieving the goals of such a plan.

Recommendation: Develop a knowledge integration tool that will describe what is known about the complex factors—from the molecular to societal levels—involved in the development of breast cancer across the life span.

This tool or set of tools would map out and integrate the complex interrelationships between the biological pathways involved in normal breast development, cellular and tissue changes resulting from adverse environmental exposures, and determinants of breast cancer. These tools also would guide the planning and prioritization of future federal programs, as well as efforts to expand interagency collaborations, Common Fund programs, and public-private partnerships. In addition, the tools would help guide communication about the accomplishments of federally funded research to the scientists and the public by describing what research is under way, what progress has been made, and current gaps in knowledge. These tools must integrate all relevant knowledge and information in a way that is easy to use and continuously update.

Examples of knowledge integration tools include the Breast Cancer and Chemicals Policy Project, High-Throughput Risk Assessment Project, and the Adverse Outcome Pathway model described in Section 7.3.4. The Committee sees continued development of these research tools as critical to identifying knowledge and research gaps, integrating what is currently known about environmental exposures and cancer, and making progress on identifying and regulating environmental exposures that affect cancer incidence. In addition, these tools will support the monitoring of progress toward understanding the associations between environmental exposures, lifestyle factors, and personal and epigenetic makeup and the risk of breast cancer.

From the context of this report, tools that are specific to breast cancer risk need to be developed and utilized to drive future federal research allocations. Developers of these tools must consider the chemical, physical, and social determinants of disease and how these influence public health interventions, health literacy, and behaviors associated with breast cancer risk. The tools should consider health disparities in breast cancer outcomes and the complex array of factors that might explain these disparities. The tools also should be able describe how factors that interact at different periods throughout the life course modify breast cancer risk. Finally, the tools need to be developed with the end goal of preventing breast cancer. This means that the model needs to incorporate components that describe how findings would move to decisions about next steps, such as testing interventions to promote protective behaviors and exposures or remediate or eliminate harmful exposures.

In developing these tools, the Committee would like to see broad participation by the research and advocacy communities. Developers are encouraged to build these tools as open, Web-based, collaboratively built and maintained, dynamic models that clearly describe our current understanding of breast cancer development. The software to support these tools could have elements of a wiki environment and incorporate elements and protocols to facilitate description of the complex processes and interactions known to play key roles in normal breast development and in the development of breast cancer. In addition, the tools need to be able to specify for each component the level of certainty based on current research findings.

Gap: Involvement of advocates and community stakeholders in the breast cancer and the environment research enterprise

Although agencies that fund breast cancer and the environment research have made substantial efforts to engage advocates and stakeholders in assessing research programs and projects, the Committee finds that these agencies need to do more to solicit advocate and community input on problems related to breast cancer, including defining program goals, generating ideas for novel research programs, designing studies, and recruiting study participants, especially for community research. Involvement of the public in research processes and decisions helps ensure research that is responsive to the public's needs, increases science literacy, and is more likely to generate knowledge that can be translated readily into culturally and language-appropriate interventions that result in improved public health.

There are three major ways that advocates and community stakeholders can be involved in research, including: (1) conducting the research itself; (2) evaluation and decision making about specific projects, research directions, and priorities; and (3) communication and translation, which is discussed in the next chapter. Advocates are not routinely involved in research activities, such as conceptualization, data collection, analysis, and report writing. There are some notable exceptions, such as CBPR, in which community residents participate in the full spectrum of research activities. This approach is described in detail in Chapter 8. Related to the role of advocates in evaluation and decisionmaking, the DoD also includes advocates in proposal reviews and requires advocate participation in some award mechanisms. In addition, a number of NIH Institutes, including NIEHS and NCI, include advocates and community stakeholders on their high-level advisory councils.

Recommendation: Continue and expand the use of advocates and stakeholders in the breast cancer and the environment research enterprise, including but not limited to participation in peer review panels and program advisory committees.

Policies to allow and foster advocate and stakeholder involvement in the research process need to be reviewed and strengthened. New policies may be needed to address challenges related to collaborative research involving both scientists and community members.[45] For example, community members might feel hindered in their ability to influence the research if there is no formal policy or process for power sharing.[46] Scientists, on the other hand, often feel that the involvement of community members

slows progress on projects and that community members may lack the scientific knowledge to contribute meaningfully.[46, 47] Such problems could be ameliorated by policy changes at funding organizations. For example, funding periods for grants might need to be expanded or restructured for projects that have significant community involvement.

The Committee, however, does not recommend requiring the involvement of community members in every research activity. The Committee calls, however, for a commitment by agencies to broader involvement of advocates and other community members in all aspects of the research enterprise. In developing these opportunities, agencies would take the lead in deciding when advocate and community member involvement is required or optional and the nature of the involvement. This should be an open, transparent process so that when advocates and stakeholders express an interest in being involved, this is considered. Agencies need to recognize the value of stakeholder participation in the research and its oversight. Consideration also needs to be given to increasing collaborations with research stakeholders and advocates representing the socioeconomic, cultural, and linguistic diversity of the U.S. public and to providing mechanisms for these individuals to have significant involvement in the design and conduct of research programs.

The Committee appreciates that it often is not easy to include stakeholders in the research; researchers sometimes resist or do not have the skills to involve stakeholders, and stakeholders sometimes face other obstacles to participation. There are many approaches that can be used to remove these barriers. This includes expanding public participation on existing federal advisory councils that review funding opportunities related to breast cancer prevention research. Scientists also can receive training to work with community members. A directory of advocates willing to participate in study sections could be compiled to enable scientists interested in engaging advocates to find a good match for their work. When possible, public participants will need training and adequate compensation so that they can fully and effectively participate in the research process.[48] Supporting advocates' travel to scientific workshops and conferences along the lines of the BCERP's annual meeting is another idea. Programs that provide resources for scientific training of community members (e.g., the SEER Breast Cancer Training Module) also help to reduce barriers to collaboration.[48]

Gap: Translating research

When research on breast cancer and the environment suggests promising interventions to reduce breast cancer risk, it will be critical to rapidly move these interventions through the translational pathway (see Chapter 8, Section 8.3.1 and Figure 8.1). These interventions must be widely adopted and sustained to maintain the progress made toward preventing breast cancer. A better understanding of the best approaches for achieving these research translation goals is needed.

Existing knowledge about effective dissemination and implementation of research findings also must reach a broader audience of researchers, health practitioners, and policymakers.

Recommendation: Support implementation science and its application.

Given the complexities of the interconnected risk factors that operate from the cellular through the societal level to lead to breast cancer, further investment in implementation science research is needed to ensure that scientific findings can be maximally translated into public health benefit.

7.9 Conclusion

A number of excellent, strong partnerships among the agencies supporting research on breast cancer and the environment have led to important discoveries in this area. The Committee expects federal agencies to continue supporting (1) research and training in breast cancer and the environment, (2) productive collaborations to address basic science issues through single-discipline and transdisciplinary research, (3) active translation of new

knowledge into products that support new interventions and public policy, and (4) innovation initiatives.

These efforts, however, should be expanded because the Committee's review of the current state of the federal breast cancer and the environment research portfolio shows that a very small proportion of current funding is focused on prevention or etiologic research. A shift in support toward prevention science and its application for breast cancer would facilitate greater understanding of the complex causal web of the disease. As noted in the overarching recommendations and the Introduction, the Committee emphasizes the importance of transdisciplinary methods and approaches that involve both scientists and advocates to advance our understanding of the role of the environment in causing and preventing breast cancer. These approaches must be incorporated into new funding mechanisms that facilitate rapid and creative responses to emerging public health issues related to breast cancer and the environment. Agencies also need to do more to support the development of a breast cancer research workforce that can collaborate effectively on the multidisciplinary teams that are needed to understand the full complexity of breast cancer and environment interactions and fill knowledge gaps.

A comprehensive research integration tool is needed to map the interrelationships between biological pathways involved in normal breast development and changes related to environmental exposures using precise and quantitative methods in animal models and human populations. This tool or set of tools also could be used to regularly record and track the accomplishments of individual laboratories and teams of scientists pursuing questions about the relationship between environmental exposures and breast cancer. Data sharing will be critical in supporting innovative, collaborative research and avoiding redundancy.

All agencies should be mindful of bringing new voices to the table for discussion. Breast cancer survivors and advocates bring a knowledgeable and unique perspective that must be included in all parts of the research process. Agencies also should consider ways to involve new scientists across the career spectrum, especially from minority communities, in breast cancer and the environment research and capitalize on existing investments in study populations that include racial/ethnic minorities, low-income women, and other underserved populations. At the same time, agencies must support implementation science research to identify the best approaches for translating scientific discoveries into interventions that can be rapidly and sustainably adopted to reduce breast cancer incidence in all communities.

In summary, to ensure that the necessary research on breast cancer and the environment is conducted, funding agencies need to place a priority on prevention research and devote funds to its conduct. Agencies must coordinate their efforts to leverage resources, particularly in these times of fiscal constraints.

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CHAPTER 8

Translation, Dissemination, and Communication of Research Related to Breast Cancer and the Environment: From Science to Society and Back Again

8.1 Introduction

This chapter explores the distinct but interrelated concepts of research translation, dissemination, and communication and their application to research on breast cancer and the environment. The chapter describes the research and theories that surround each concept and discusses strategies for effectively translating, disseminating, and communicating research findings to prevent breast cancer. Existing projects that focus on breast cancer and environmental health, particularly community-based projects, provide models that can be expanded and applied to this area of research. The chapter includes recommendations that emphasize the involvement of relevant stakeholders—including but not limited to environmental and breast cancer advocates—in the translation, dissemination, and communication of relevant research. These stakeholders must reflect a diversity of races, ethnicities, cultures, and social classes. Such stakeholders can help to shape research projects to ensure effective translation of findings into interventions, policy decisions, and bidirectional dissemination and communication efforts that support the ultimate goal of breast cancer prevention. The chapter concludes with a discussion of policy implications for the translation, dissemination, and communication of research on breast cancer and the environment.

> Research on environmental exposures that affect breast cancer development, progression, and mortality must be translated into effective prevention action and policies.

It is imperative that the scientific findings from studies of breast cancer and the environment be translated into action. Numerous stakeholder groups are invested in this area of research because of its potential to reduce the burden of disease through the application of knowledge. Engaging these stakeholders early in the research process, as discussed in Chapter 7, can enhance the quality and relevance of the research and sets the stage for more effective research translation, dissemination, and communication. Research translation, dissemination, and

communication do not begin or end with the publication of the scientific data. Effective translation activities must begin well before publication [1] and should start with a systematic analysis of audiences and the optimal pathways for disseminating and communicating results to each audience.

Effective tools and strategies for translating, disseminating, and communicating research are necessary to achieve the IBCERCC's mandates to: (1) improve existing research and develop comprehensive strategies that expand and deepen transdisciplinary and innovative research, (2) reduce duplication of effort across agencies, (3) increase the involvement of patient advocacy and community organizations that represent a broad geographical area, (4) improve the dissemination of information on progress in breast cancer research, and (5) further develop public/private partnerships to advance collaborative, cross-cutting research. Improved research translation, dissemination, and communication also can foster policy change, which offers the potential to create lasting changes in the health environment at the community, local, and national levels.

8.2 Importance of Public Participation

Advocates began public discussions about breast cancer nearly 40 years ago. Advocates and community stakeholders continue to provide a diversity of voices and perspectives on a disease that currently strikes 1 in 8 women in their lifetime and increasingly affects men in this country, with a disproportionate impact on women of color and other minorities. Many advocates are survivors—women and men—who are living with a diagnosis of breast cancer, along with their families, friends, health care providers, and co-workers, all of whom live with the effects of breast cancer on their lives. Advocates play a critical role in the effective translation, dissemination, communication of research findings by serving as interpreters, communicators, and policy contributors.

As discussed in Chapter 4, breast cancer survivors, local and national advocacy organizations, and health practitioners have long played a key role in drawing attention to breast cancer and its devastating effects by focusing on screening, treatment, access to care, and survivorship issues. In the early 1990s, breast cancer advocates called for breast cancer prevention and expanded the conversation beyond screening, treatment, access to care, "known risk factors," and potential cure to the complicated issue of the causes of breast cancer, especially environmental causes. Advocacy expanded to include environmental public health and justice groups who called for policy changes in response to a growing, compelling body of evidence on the possible associations between breast cancer and environmental exposures. In response, federal agencies formed innovative research partnerships and collaborations that included advocates and scientists and resulted in new models for advancing research on breast cancer and the environment.

In the early 1990s, breast cancer advocates called for breast cancer prevention and expanded the conversation beyond screening, treatment, access to care, "known risk factors," and potential cure to the complicated issue of the causes of breast cancer, especially environmental causes.

The National Cancer Institute (NCI) and National Institute of Environmental Health Sciences (NIEHS), for example, partnered with local breast cancer advocates in New York and Connecticut during the Long Island Breast Cancer Study Project to explore the rising rates of breast cancer in local communities.[2] The NCI and NIEHS held public meetings with breast cancer advocates and other members of the public. The investigators also provided regular updates on study progress to the Long Island Breast Cancer Network consortia of advocate and civic groups concerned about the high rates of the disease in their area. This project marked the early engagement of advocates in the research process that focused specifically on breast cancer and

the environment. The NCI and NIEHS collectively expanded this collaboration model to include advocates across the country when it launched the Breast Cancer and the Environment Research Centers.[3] Breast cancer advocates contributed to the development of BCERC grant proposals in partnership with scientists. These partnerships continued through participant recruitment, report back of initial results to participants, and ongoing efforts to disseminate and communicate research findings.

Now in its second phase, BCERC has evolved into the Breast Cancer and the Environment Research Program[4] and incorporates a transdisciplinary network of scientists, clinicians, and community partners who seek to understand the windows of susceptibility when the developing breast is more vulnerable to environmental exposures. The Sister Study[5] and the Two Sister Study[6] are other examples of research activities that reflect NIEHS' commitment to examining the environmental causes of breast cancer and to recruiting women of color and other minority populations who often are understudied and underrepresented in breast cancer research. The breast cancer advocacy community assisted in recruiting more than 50,000 sisters for these studies. These recruitment efforts required consideration of how research findings could be communicated clearly to the public and translated into actions to protect public health. The Sister Study relied on a variety of print and digital media to communicate its goals and recruit participants.

The Sister Study and the Two Sister Study have recruited more than 50,000 sisters and will study breast cancer in women of color and minority populations.

The Centers for Disease Control and Prevention (CDC) partnered with breast cancer, environmental, and women's health advocates on multiple efforts that resulted in increased funding for the CDC's National Environmental Health Biomonitoring Laboratory[7, 8] and for state biomonitoring programs.[9] The CDC and NIEHS also funded and worked with advocates to organize the first International Summit on Breast Cancer and the Environment.[10] More recently, the CDC and the Agency for Toxic Substances and Disease Registry (ATSDR) engaged a broad range of stakeholders—including government agencies, professional organizations, tribal groups, community and nonprofit organizations, health professionals, business and industry leaders, and members of the public—in the National Conversation on Public Health and Chemical Exposures. The CDC and ATSDR followed up on this multi-stakeholder activity by releasing an Action Plan based on the National Conversation.[11]

Breast cancer advocates also have worked with state legislators to secure funding for independent research programs that address breast cancer and the environment, including the California Breast Cancer Research Program[12] and the Massachusetts-based Silent Spring Institute.[13] Advocates and scientists have worked together in networks as diverse as the Collaborative on Health and the Environment,[14] which provided testimony for the President's Cancer Panel report *Cancer and the Environment: What We Can Do Now*[15] and Vassar College's Environmental Risks of Breast Cancer CD_ROM and Web-based interactive educational tool.[16] Breast cancer advocates and organizations also played a major role in calling for the Breast Cancer and Environmental Research Act of 2008 as well as the Institute of Medicine (IOM) report on *Breast Cancer and the Environment: A Lifecourse Approach*.[17]

Collaborations between breast cancer researchers and advocates facilitate efforts that effectively respond to public needs and concerns, accelerate the application of research findings in clinical practice, communicate scientific evidence to the public in a meaningful way, and lead to policy decisions that support breast cancer prevention. The types of advocates who participate in prevention research, however, may differ from advocates who participate in treatment research. Most prevention research

on promoting or ensuring public health; therefore, those who are healthy have the most to gain from this research. Treatment research, on the other hand, focuses on treating those who are ill, so those who are affected by the disease have the most to gain from this research.

8.3 Research Translation, Dissemination, Communication

8.3.1 Research Translation—From Theory to Practice

During the past 2 decades, science, public health, breast cancer, and environmental health and justice sectors have called for collaborative, transdisciplinary research on:

- Exposures,[18]
- Chemical safety evaluations,[19]
- Translation of studies of the environmental effects of disease into clinical practice,[20]
- Risk management and regulatory action, and
- Environmental public policy for health promotion.

An expanding body of evidence underscores the need for research translation.[21-27] Graham and colleagues[22] described a knowledge-to-action gap that encompasses the use of scientific knowledge by practitioners, policy makers, and the public. A review by Green, Ottoson, Garcia, and Hiatt[28] also indicated that scientific data continue to be inadequately applied to clinical practice. Green and colleagues cited data suggesting that only 14 percent of biomedical research affects patient care and that the time lag between discovery and application is 17 years on average. This time lag applies to clinical medicine and might be different for public health interventions.[28] Considering that windows of susceptibility to environmental risk factors may occur early in life for breast cancer, rapid translation of science into preventive public health actions could have striking impacts on breast cancer incidence in the future.

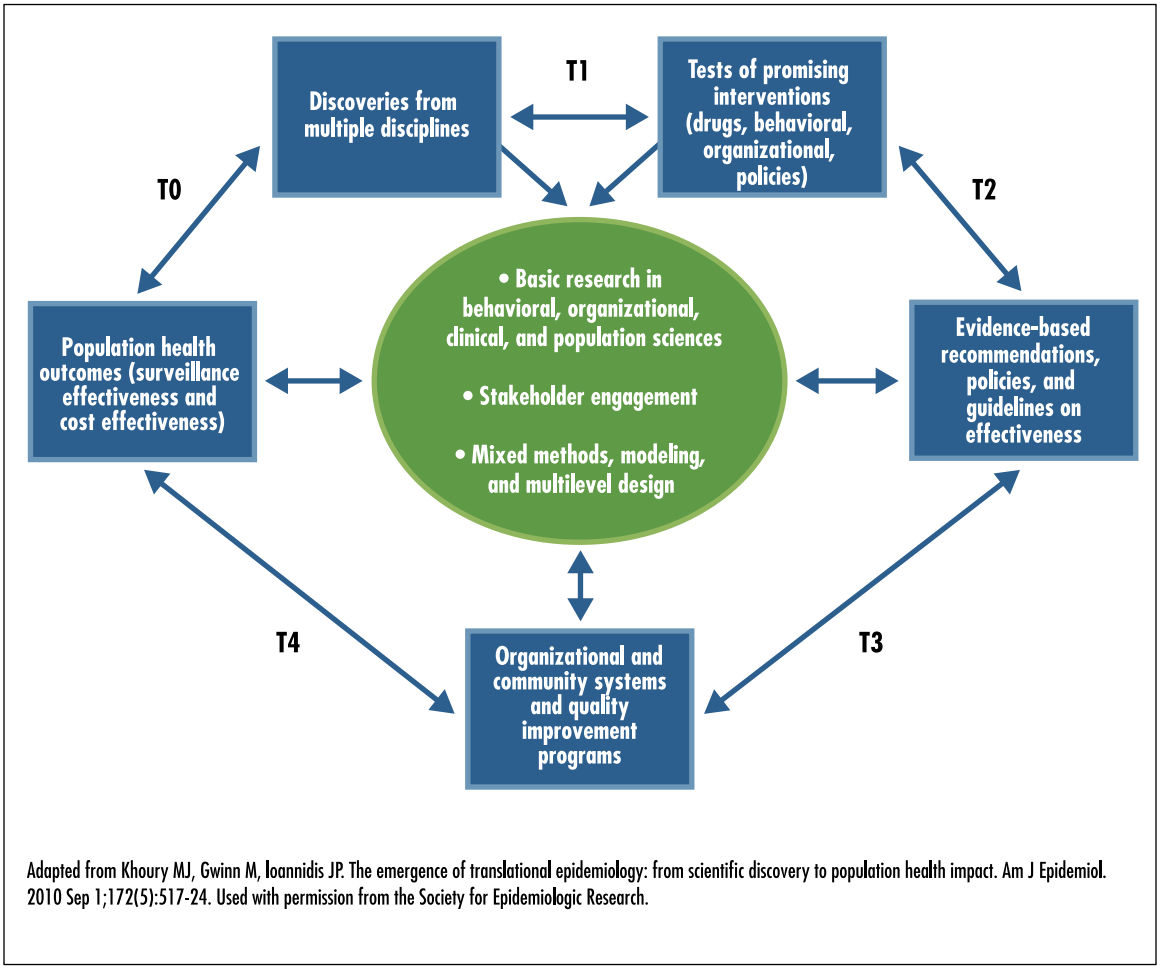
Currently, only 14 percent of biomedical research affects patient care and the time lag between discovery and application is 17 years on average.

Shortening the knowledge-to-action gap requires specific strategies. The model of research translation in Figure 8.1 provides one framework for translating basic discoveries into public health approaches that can be implemented and sustained in real world settings.[29] Data can be gathered at each of the four phases described in the framework to evaluate whether translation efforts are effectively protecting public health. Furthermore, implementation science (described in Chapter 7) can help identify strategies for expanding and promoting prevention activities that have the best chance of rapidly, effectively, and sustainably improving public health. Application of research translation strategies identified through implementation science will help ensure that knowledge is shared and used in ways that provide the greatest benefit to society.

Research findings relevant to breast cancer and the environment vary in the degree to which they have been translated into effective prevention activities. For example, interventions designed to increase physical activity have been applied to evidence-based guidelines and evaluated in multiple studies.[30-32] Further efforts are needed to evaluate and tailor physical activity programs for diverse communities and to address barriers to physical activity.[33,34] On the other hand, few interventions to reduce exposures to environmental chemicals suspected of increasing breast cancer risk have been developed and generally are not applied to clinical practice or public health policy.[35]

The most effective research translation programs are those that engage investigators from multiple disciplines, include community stakeholders, and encourage the use of participatory and action-based methods[36] and bi-directional approaches.[27, 37] Seeking solutions across disciplines can promote innovation and increase the impact of research findings[21]

Figure 8.1. Knowledge integration process



Adapted from Khoury MJ, Gwinn M, Ioannidis JP. The emergence of translational epidemiology: from scientific discovery to population health impact. Am J Epidemiol. 2010 Sep 1;172(5):517-24. Used with permission from the Society for Epidemiologic Research.

Glasgow, Vinson, Chambers, Khoury, Kaplan, and Hunter[29] developed a dynamic, non-linear model for translating research into public health action. This model, adapted from a model developed by Khoury and colleagues,[38] presents four related stages of research translation. Basic discovery of determinants of health outcomes from behavioral, organizational, clinical, and population science; mixed methods research; and stakeholder engagement are at the center of the model and influence all stages of translation. The inter-related stages of translation are defined as follows: T0 – the discovery that presents an opportunity to improve health; T1 – research that develops clinical, public health, policy, social, and behavioral interventions; T2 – rigorous testing of interventions to determine their ability to improve health outcomes; T3 – research to increase the translation of the intervention into practice; and T4 – evaluation of the effectiveness and cost-effectiveness of interventions in real world settings and in diverse populations.

by making them available to the right people, in the right locations, at the right time.[36] As Portier and colleagues pointed out, "The problems of modern society only become more complex over time; similarly, the science required to address these problems, particularly in the area of human health and disease, is increasingly complex." Responses to social and scientific complexity that encourage stronger and more "permeable" interactions[23] among scientists, regulators, medical professionals, public health officials, advocates, and communities will promote improvements in research translation and application.[27]

To summarize, sustaining active research translation efforts can lead to improved clinical and public health practices and policies to control exposure to environmental risk factors and reduce disparities in exposure that ultimately will reduce breast cancer. Furthermore, engaging community stakeholders in the research process will enhance active translation efforts because these individuals and groups can effectively disseminate breast cancer prevention interventions to many audiences.

8.3.2 Research Dissemination—Letting the Public Know

Research translation requires an effective exchange of information within and between networks of funding agencies, researchers, advocates, and other stakeholders. The exchange of information can be enhanced by active dissemination efforts to ensure that science enters the public domain accurately and reaches those stakeholders who are invested in breast cancer prevention.

Dearing and Kreuter[39] encouraged dissemination efforts that both *push* information to intended users and involve *pull* (also referred to as "diffusion") strategies that engage with users' needs so that they are drawn to the information. Dearing and Kreuter distinguished between dissemination strategies that make information available and diffusion strategies that encourage stakeholders to use knowledge. Implementing diffusion strategies requires an understanding of stakeholders' needs prior to dissemination actions and an ability to take advantage of existing influence and relationships among people and organizations. The goal of dissemination is to use knowledge in ways that improve population health and well-being. For push-pull strategies to be implemented and effective,

Active dissemination efforts are needed to ensure that science enters the public domain accurately and reaches those stakeholders who are invested in breast cancer prevention.

a third element—capacity—also is required. Capacity creates the necessary infrastructure to deliver knowledge and can include training, technical assistance, policy setting, and cost analysis.[39]

The following strategies can help create the infrastructure needed to implement dissemination efforts that integrate "push and pull" approaches. These strategies can be used alone or collectively.

- **Engage intermediaries:** Nieva and colleagues[40] recommended creating dissemination partnerships that link "knowledge and resources" (researchers and knowledge distillers) with potential intermediaries (individuals and organizations that can function as knowledge brokers and connectors to practitioners and delivery organizations in the health care system). These partnerships can bring together science-based knowledge and what is known about the context, motivations, and constraints of knowledge users. Intermediaries also can help move research to practice,[40] policy,[41,42] communities,[43] and public health interventions.[28,38]

Dissemination of research must push information out to intended users and pull users in to utilize the information.

- **Conduct outreach to stakeholders:** Participatory approaches and partnerships that engage a wide range of stakeholders in the development and implementation of dissemination strategies have the advantage of accessing the understanding of various communities. This approach increases the relevance of interventions and their interest to the targeted communities. Partnerships with target communities also facilitate the use of existing information distribution systems and networks within communities to reach specific audiences. Community participatory approaches to disseminating research findings (these approaches engage communities and advocates early and throughout the research process) lead to communication innovations that are "wanted, regularly used, and are more likely to sustain."[39] Participatory approaches also may facilitate the dissemination of research to minority communities and communities that lack resources when those groups are included early and can help to shape projects.

- **Employ structured plans:** Structured plans that consider potential dissemination pathways are another strategy for effective dissemination. The concept of dissemination pathways, originally formulated in the renewable natural resources literature, refers to the routes or channels by which information and technology reach users of scientific evidence.[44] Dissemination pathways are

- context-dependent, interconnected, and multidirectional and can include researchers, funders and other agencies, advocates (including partners in community-based participatory research [CBPR] projects), community leaders, lay people, and the media. For example, advocate partners in studies can provide pathways for communication through community leaders to the larger community or network of lay people. Well-constructed dissemination plans and pathways also can help to identify partnerships that will facilitate interagency data sharing in ways that advance the fields quickly.

Funding agencies can promote research dissemination by requiring researchers to report back to funding agencies about anticipated publication of findings that likely will generate high public interest, have controversial implications, or suggest public health actions. This sharing of information can enable collaborations among researchers, funding agencies, advocates, and other stakeholders to develop coordinated dissemination strategies and help ensure that research findings reach those who need this information in ways that are timely, effective, and responsive to community concerns.

8.3.3 Research Communication—Helping the Public Understand

Early communication of research implications allows representatives from different communities to identify concerns and communicate them to the scientific community. This feedback from the end-users of research findings allows funding agencies, researchers, and other collaborators to develop appropriate strategies for responding to community concerns.

Research related to issues of public interest, such as environmental exposures and breast cancer, likely will be communicated by individuals with a broad range of perspectives on the science. Because communication often occurs with or without the researchers' active engagement, researchers and funding agencies should ensure that the best possible information is available to stakeholders in real time. Strong relationships between scientists and other stakeholders must be formed to ensure that the science is communicated accurately and with clear messages about the ways in which science can aid in decision making.

Scientists must be ready to engage, explain, and respond to the public and to messengers in a timely manner and with a consistent message.[45] This can be facilitated by providing scientists with training and tools. For example, Web-based resources and guidelines can help scientists tailor the communication of their findings to certain public or intermediary audiences, who then convey the research findings to a wider public while maintaining accuracy. Messages should focus on the most important results and on conveying the principal implications of the findings.[46] Communication also must find a balance between asserting the implications of findings and recognizing the limitations of the data. Collaborations among scientists and other stakeholders can help reach this balance. The Committee reviewed numerous resources on research communication and concluded that utilization of the "toolkit" model will best serve communication of research on breast cancer and the environment. Appendix 5 references those resources and outlines potential activities, outputs, impacts, and best practices for inclusion in a toolkit.

8.3.4 Communicating Results to Study Participants

One important area of research communication, the reporting of research results to research subjects, involves issues of ethics as much as communication. The growing consensus is that policies are needed to guide researchers in reporting study results back to participants. These policies also can establish the requirement that resources be devoted to report-back and help establish criteria for institutional review boards to implement. Researchers repeatedly have highlighted the ethical need to report back exposure information to research participants.[47-49] For example, the BCERP's 2011 annual meeting included a panel discussion that focused on lessons learned in the first 7 years of the BCERC's study results,[50]

including a case in which unexpected biomonitoring results prompted report-back to participants and the community.[48]

Research concerning exposures raises ethical questions when the health effects of the exposures are uncertain or unknown, and when it is unclear what exposure level is a threat to health.[48, 51] Exposure assessment researchers should clarify to participants the types of information that a study can and cannot provide. Reporting the results of exposure studies is necessary to increase transparency and build trust. Brody and colleagues[47] suggested using CBPR models that involve teams with diverse perspectives and training to facilitate decision making concerning report-back of exposures with unknown health effects. The importance of building trust and responding to the needs and concerns of affected communities through partnership, report-back, and transparency throughout the research process is underscored by the historical legacy of harm, unequal treatment, lack of responsiveness to community concerns, and lack of community involvement in decisions regarding environmental regulations.[11,52] Institutional review boards must be attentive to CBPR and report-back ethics to empower community involvement in research projects.[53] Effective methods of representing individual and study cohort exposure data in an understandable format have been developed by the Silent Spring Institute[47] and have been adopted in other settings.[48] These methods involve explaining individual results graphically by displaying them on a chart relative to others in the study cohort. Often, nationally representative exposure data from the National Health and Nutrition Examination Survey also are indicated as a reference point. Researchers and participants may experience a false sense of security, however, when an individual's or community's exposure levels are at or near those measured in the population as a whole.[54] This potential misperception raises ethical issues because population exposure could be at levels that may create health risks, but a favorable comparison to national levels could lead to a view that no action is needed to ameliorate the exposure.

8.3.5 Dialogue With Multiple Audiences About Breast Cancer and the Environment

Increasingly, science communication is framed as a dialogue[55] or as bidirectional,[56] as opposed to simple transmission from scientists to the public. Dialogue can help to answer questions or assuage public fears about technology, new areas of research and scientific discoveries, and extrapolations from animal models to humans in environmental research. Furthermore, the public may have important knowledge about local exposures from agriculture, industry, or waste sites; or about broad social concerns regarding environmental exposures and breast cancer. This knowledge can provide researchers with vital insights, but is uncovered only through dialogue.[56] In addition, as community members learn to ask the right questions and become knowledgeable about scientific vocabulary and concepts, their contributions can strongly support scientific research.

The dialogue approach also provides members of the public with knowledge that allows them to avoid exposures of concern. Scientists, on the other hand, gain allies who can translate, disseminate, and communicate findings and who engage in efforts that call for precautionary public health policies for breast cancer prevention and additional funding for research.

One example of an effective bidirectional communication effort is the University of North Carolina's Community Outreach and Education Core (COEC), a project of the School of Public Health. The COEC has held breast cancer workshops in the local community since 2002, using case studies to demonstrate breast cancer risk factors. Based on dialogue with African American lay health advisors, COEC scientists simplified case studies and created "breast cancer risk bingo," an educational activity to engage community members.[57] Since 2004, educational efforts using bingo also have been effective in Latino communities.[58]

BCERP also has used bidirectional communication between academics and communities to increase responsiveness to community needs. For example, via "tea talks," the Bay Area BCERP discovered that families were interested in learning about their daughters' biomonitoring results, which were collected as part of the research project. In response to the community's interest, the Bay Area researchers and Community Outreach and Translation Cores (COTC) undertook a project to provide families with the study results.

8.3.6 Tailoring Communication to the Audience

The 2011 IOM report on Breast Cancer and the Environment recommended that research be directed at identifying effective risk communication approaches for multiple audiences, including the general public, health care professionals, and policy makers. The IOM determined that multiple communication strategies, modes of communication (e.g., technologies), and messaging tactics would be necessary to reach diverse communities.[17]

When developing and implementing communication approaches for specific audiences, audience segmentation can help communicators determine how and when to share findings.[46] For example, communication plans should consider the information requirements of policy makers in making decisions, the time constraints of journalists for publishing a story, the needs of health professionals to answer patients' questions, and advocates' responsibility to relay information to their constituencies.

Developers of communication approaches must pay attention to culturally and linguistically appropriate messaging. Following a long-term project directed by the U.S. Department of Health and Human Services (HHS) Office of Minority Health to nationalize standards around Culturally and Linguistically Appropriate Services (CLAS), the federal government adopted and published the standards in March 2001. The standards require that "materials in commonly encountered languages should be responsive to the cultures as well as the levels of literacy of patients/consumers."[59] Linguistic translation should include translation by a trained individual and review by target audience groups. Furthermore, if scientific research materials are to be used and understood, they must be easy to read and attractive to the audiences they are meant to reach.

Surveys have shown that nearly one-half of U.S. adults read at basic levels, and one in five U.S. adults reads below a fifth-grade level.[60] Perhaps more importantly, many Americans have limited health literacy, a basic set of skills that people need to adequately function in the health environment. Limited health literacy is associated with poorer use of health care and poorer health outcomes.[61, 62] The ability to understand numbers, called numeracy, also is important in understanding risk.[63] Communicating about risk requires thoughtfully tailored communication plans to convey complex concepts of relative numbers and population-based statistics.[63] Differences in reading ability, health literacy, and numeracy suggest that the best methods for communicating risk may vary depending on the audience.[64]

Multiple communication modalities can be employed to target specific audiences that want or need to know about exposures, risks, and preventing breast cancer. These modalities provide a channel to communicate with hard-to-reach audiences and include word-of-mouth, television, radio, print materials distributed at various locations, or electronic materials in diverse formats and accessible in different ways (e.g., through social networking sites).[55]

The tailoring of research communication activities and products to convey research findings to the public and specific audiences will be influenced by the nature of the research. For example, what is communicated about a cellular mechanism research project will be very different from what is communicated about a longitudinal cohort epidemiology study.

8.3.7 New Technologies in Research Communication

Modern technology creates the potential to reach wider audiences, both within peer groups of scientists and the population as a whole.[65] Peer-reviewed journals alone usually do not suffice to communicate findings within the scientific community or to lay audiences. Stakeholder engagement can help to create pathways to reach lay communicators, who often are well connected online and can serve as an excellent resource for reaching wider audiences with clear, accurate messages about research findings.

Print, broadcast, and online communication channels can broaden the reach of scientific messages.[55] Online tools such as social media, blogs, and video websites could be used to more effectively disseminate new research and provide evidence-based responses to concerns regarding environmental and breast health.[11]

Web-based collaboration tools also can facilitate bi- and multidirectional communication. These tools can be used for collaboration, document sharing, and presentation to geographically dispersed audiences in real time. For example, Dubé and colleagues[66] recommended using technology to create virtual communities of practice (vCOPs). This concept has been used in business and international governance and could be applied to clinical and public health practices to support breast cancer prevention.

Smart phones, e-readers, tablets, and other devices allow many individuals nearly constant access to information through social media, news feeds, and visual- and image-driven media and apps. Use of these technologies holds considerable promise for health communication, behavior change interventions, and research.[67, 68] An example of the use of these technologies for health communication is the American Society of Clinical Oncology's cancer.net app for iPhones and iPads (see http://www.cancer.net/multimedia/mobile-applications), which provides valuable information for cancer patients in multiple media formats as well as enabling users to record symptoms as they occur, store medication information, and submit questions to specific physicians in voice or text format.[69] A wide range of smartphone apps also has been developed to promote behaviors that may help prevent breast cancer (see http://www.mdanderson.org/publications/focused-on-health/issues/2011-july/mobileappscancer.html). Although smart phones and related devices are the preferred methods of communication for many people, options should exist that allow individuals to access information on desktop computers at libraries and community centers.

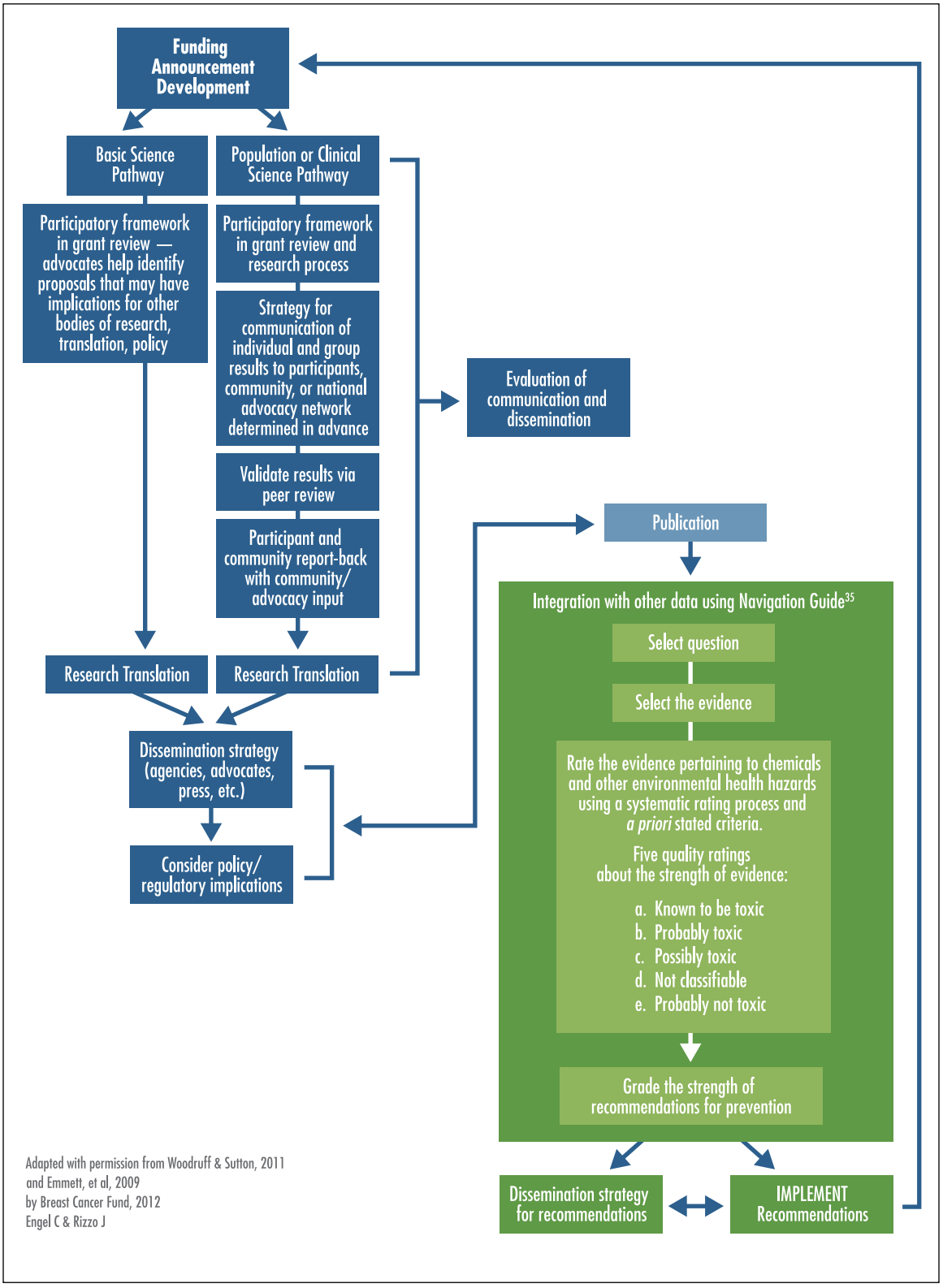
To reach the next generation of scientists, effective and honest communication of science will require the use of new media. Space limitations and journal conventions limit the capacity for articles to provide a complete research picture. Journals that resemble video collections may communicate findings more effectively. For example, *The Journal of Visualized Experiments* provides an interactive, video-based journal that is referenced in PubMed and other scholarly databases.[70]

8.3.8 Research Translation: Conclusion

Publication is not the final step in the process of sharing research findings, as shown in Figure 8.2. Instead, new findings can be integrated with other relevant findings using Woodruff and colleagues' 2011 navigation guide.[35] This guide offers a process for selecting and evaluating the weight of the evidence across relevant disciplines and then developing recommendations. Recommendations can, in turn, be assessed for their capacity to be implemented and to meet consumer preferences and needs. Like research findings, recommendations also need to be implemented widely so that they can affect regulation, market-based policies, consumer choices through public education, and future research directions.

In summary, attaining the goals of research translation, dissemination, and communication requires the engagement of stakeholders early and throughout the research process. Stakeholders can contribute

Figure 8.2. Research translation, dissemination, and communication pathways for stakeholder engagement



The above model illustrates opportunities for advocate and community stakeholder engagement from the beginning stages of research through translation, dissemination, and communication of research findings. The model illustrates that these stakeholders can play a role in all phases of research and can help ensure that findings are translated into policy and recommendations for prevention.

insights about community concerns, research priorities, and knowledge gaps regarding breast cancer and the environment. The model shown in Figure 8.2 illustrates the opportunities for engaging stakeholders at different phases of research. These opportunities extend beyond publication into knowledge integration and the development and implementation of recommendations for prevention. Recommendations can influence policies, market-based practices, and future research. Stakeholders also may help to recruit study participants and with engaging and reporting research findings to communities and individuals. Strategies and plans for communicating and disseminating findings and their research translation implications need to be developed early in the research process (i.e., no later than the period immediately after research is completed but before final publication of findings). These strategies should include dissemination plans directed at research participants, broader groups of stakeholders, and the media.

8.4 Examples of Research Translation, Dissemination, and Communication in Action

A number of research and clinical programs relevant to breast cancer and the environment have integrated goals and activities related to research translation, dissemination, and communication. The most effective programs:

- Have formal structures for translation, dissemination, and communication;
- Use participatory approaches for involving stakeholders;
- Provide funding for advocates and community involvement;
- Consider environmental justice issues; and
- Conduct evaluations.

The following examples demonstrate how these strategies have been applied to enrich programs or projects.

8.4.1 Formal Structures for Translation, Dissemination, and Communication

A translation, dissemination, and communication structure was created when the BCERCs were established in 2003 by the NIEHS and NCI with a 7-year funding cycle. The BCERC used a national transdisciplinary network of scientists, breast cancer advocates, and community members to plan, implement, and disseminate the findings from basic research and prospective cohort studies of girls as part of a coordinated effort to understand the effects of environmental exposures on the sequence of puberty. The BCERCs involved advocates at all phases of the research process through COTCs and community partnerships. The prospective, longitudinal nature of BCERC epidemiologic studies has been particularly conducive to translational activities. In September 2009, using American Recovery and Reinvestment Act (ARRA) funds, the NIEHS contracted with a communications firm to help develop key messages derived from BCERC/BCERP research and incorporate the messages into communication toolkits for multiple target audiences.[71] The NIEHS and NCI also have demonstrated continuing commitment to strengthening the academic-advocate partnership that was formed as part of the BCERC/BCERP program by scheduling meetings and conference calls with these two groups to develop communication and dissemination publications.

The CBCRP is another excellent model of research translation. The program requires that funding applicants place research projects on a "critical path" that leads from "basic concept to a measurable impact."[72] Research translation was a key priority of this program, which drew from applied research literature[73, 74] to create three critical paths that apply to the disciplines of (1) clinical research; (2) behavior change and supportive services; and (3) other disciplines, including environmental research. The three context-specific versions of the critical path specify that translation efforts be adapted for a variety of audiences and desired outcomes. The approach also involves stakeholders in policy implementation and

demonstrates how advocate involvement can ensure that resulting health policies meet the program's aims.

Environmental health programs not directly related to breast cancer can provide excellent frameworks for developing and implementing strategies to translate breast cancer and the environment research. The EPA-funded Pediatric Environmental Health Specialty Units (PEHSUs), a coordinated effort between the Association of Occupational and Environmental Clinics and ATSDR, is one such program. PEHSUs include health care professionals across North America with specialized knowledge in pediatric environmental health. These units serve as a resource for translating research on environmental health into clinical practice. The PEHSUs partner with national organizations and train pediatricians in environmental health practices and communication of current environmental health information to the public. PEHSUs could serve as a model program for exploring ways to disseminate information about childhood exposures that could be precursors of disease later in life, including breast cancer.

An interagency collaboration can focus on the design, development, and implementation of formal structures for the effective translation, dissemination, and communication of research findings. Several federal public health communication projects have underscored the value of coordinated efforts to identify targeted stakeholders and a commitment to share research findings with other agencies and stakeholders.[75-77]

8.4.2 Participatory Approaches for Involving Stakeholders

Participatory approaches are increasingly common in epidemiologic, community-based, and other human studies of environmental links to breast cancer. The CBCRP evaluated research awards focused on community research collaboration and found that involving multiple stakeholders facilitates better dissemination of research findings and more effective communication.[78] The BCERCs also effectively integrated community-based projects that facilitated the dissemination of research findings to participants and communities,[48, 79, 80] and planned to continue to integrate community projects as part of the extended funding for the BCERP. In addition, NIEHS programs frequently integrate CBPR principles through the Translational Research Programs.[81]

CBPR is an effective participatory approach that involves ". . . scientific inquiry conducted in communities and in partnership with researchers. The process of scientific inquiry is such that community members, persons affected by the health condition, disability or issue under study, or other key stakeholders in the community's health have the opportunity to be full participants in each phase of the work (from conception→design→conduct→analysis→interpretation→conclusions→communication of results). CBPR is characterized by substantial community input in the development of the grant application."[82] The CBPR model is appropriate for projects that are based in specific geographic locations or that can clearly define the parameters of geographically dispersed communities with shared affiliations. Examples of these types of projects include the Nurses' Health Study[83] or the Child Health and Development Studies,[84] which draw from a multigenerational cohort of Kaiser Permanente members around the United States. CBPR models have been applied to environmental health research and communication efforts in Appalachian American communities concerned with air quality;[56] African American and Latino communities in Harlem working to reduce diesel exhaust and improve air quality;[85] Latino communities in San Diego as part of the Toxic Free Neighborhoods Campaign;[86] communities of primarily Latino agricultural workers concerned about pesticides in central Washington state;[87] and communities affected by perfluorinated compound pollution in Appalachian Ohio.[1] Because communities can be heterogeneous and individuals can be a part of multiple communities, CBPR should allow "community" to be defined by the people whose health may be affected by the research.[81] Community can refer to neighborhood, religious affiliations, racial or ethnic group membership, age cohort, sexual identity, or a disease-affected group.[77]

Reaching opinion leaders in communities through CBPR or other methods may be important. This is particularly true when attempting to reach communities that are underserved because of language and/or cultural barriers, mistrust of conventional information sources including government, or because members have little interest in certain scientific issues.[55]

8.4.3 Funding for Advocates and Community Involvement

The strongest examples of research translation, dissemination, and communication in action not only involve advocates early in the research process, but also provide strong guidance and ensure that advocates are adequately compensated. The CBCRP program seeks to fund projects with community-based and research translation activities by advocates and includes line items in the budget to compensate advocates for their time and investment in projects. The program strongly emphasizes advocate involvement in research practice, policy outcomes, and translation through its grant proposal format and grant review process. Advocates are involved throughout the research process, including review of proposals.

CBCRP instituted a Letter of Intent (LOI) process in 2006 to ensure that proposed projects fulfilled the program's research translation goals to achieve practical outcomes in humans. This process had the added benefit of reducing the number of proposals to a reasonable level given the funding limitations. In 2010, the CBCRP Council further refined the LOI process to emphasize the program's commitment to including advocates in grant application procedures and notified all principal investigators with approved LOIs that advocate involvement was required. This simple action resulted in a dramatic increase in advocate inclusion and all grants funded in 2011 met the requirement of including advocates as funded contributors in projects.[88] Other programs could institute similar LOI processes to ensure that funded projects recruit, retain, support, and compensate advocates and community members involved in research projects.

8.4.4 Environmental Justice Considerations

Environmental justice continues to be a broad public health issue and has not been integrated adequately into research, public health actions, or regulatory policies related to breast cancer. Examples of effective projects and programs that seek to alleviate environmental injustices, however, do exist. The programs discussed in this section examine the scientific data on environmental exposures and also look beyond the science to social concerns such as poverty, racism, and other issues that contribute to environmental risk. These programs often engage the community using principles of CBPR (described in Section 8.4.2), which lead to multiple benefits for researchers and community members, including: (1) increased trust between researchers and community members; (2) increased relevance of research questions; (3) increased quantity and quality of data collection; (4) increased use of and relevance of data; (5) increased dissemination of research findings; (6) translation of research into policy; (7) emergence of new research questions; (8) extended research and interventions beyond those considered at the start of a project; and (9) improved infrastructure that builds the capacity of communities to sustain project benefits and implement new research projects of longer duration and larger scale.[81]

One such program is the CBCRP, which has made considerable efforts to fund projects in areas where there are research gaps with regard to environmental exposures, health disparities, prevention, and translation and community-based projects. Despite research priorities, grant applications in these areas were few, leading the CBCRP to develop a Special Research Initiatives (SRI) program.[89] The SRI sets aside specific funding for projects that focus on environmental justice and health disparities. SRI grant proposal review criteria include assessment of the proposed project's relevance to environmental health and prevention issues and potential to stimulate research in these areas. The SRI has funded multiple research projects that have expanded the body of science in the areas of environmental health and prevention.

NIEHS' Partnerships for Environmental Public Health (PEPH) program also focuses on environmental justice by supporting research that promotes communication and collaboration among many "fenceline" communities (communities in close proximity to industry or waste sites). PEPH brings together scientists, community members, educators, health care providers, public health officials, and policy makers to collaborate in advancing the impact of environmental public health research at the local, regional, and national levels.[90]

The NIH and EPA also have collaborated to support communication on environmental justice issues through the Environmental Justice Partnerships for Communication grant program. Projects supported by this program have linked community members with researchers and health care providers, helped increase awareness of environmental health issues, shaped research policy, and identified problems and developed solutions (including a project to connect breast cancer advocates with environmental justice concerns). These activities led to improved public health by providing farm workers in California with warm water for hand washing (culturally considered good for health) and lightweight clothing to protect workers from pesticides.[91] These actions reduced the pesticide residues carried into workers' homes. Another project focused on training nurses and community asthma specialists in techniques for improving asthma management in King County, Washington.[91]

Another project to link exposure assessment, environmental justice, and breast cancer advocacy illustrates the power of community-based projects to directly affect community exposures. The NIEHS funded a partnership between the Silent Spring Institute; Brown University; University of California-Berkeley; and Communities for a Better Environment (CBE), an environmental justice organization based in Richmond, California (home to a Chevron oil refinery). At the time of the study, the refinery was seeking to expand production, a proposal that had an already environmentally burdened community concerned about increased exposures. The project team conducted an exposure study using coastal Bolinas, California as a comparison. Relative to Bolinas, more chemical compounds were detected in the outdoor air in Richmond. In addition, high concentrations of 33 compounds were detected in Richmond compared to a high concentration of one compound in Bolinas. The elevated levels of compounds in Richmond were anticipated to be markers for additional unmonitored and uncharacterized compounds. At the time of the study, CBE mounted testimony against the proposed refinery expansion. The study led to a hold on the plant's expansion. (See Brody, 2009[51] for a full account). Participants' personal indoor exposure data also were reported to them, which helped to engage the community.

In 2012, the HHS released an Environmental Justice Strategy and related implementation plan. In developing the plan, HHS held the vision of "a nation that equitably promotes healthy community environments and protects the health of all people." The strategy builds on existing collaboration across HHS agencies and was developed with the engagement of multiple stakeholders to create a plan that would respond to community concerns. The Committee concurs with the values expressed by the HHS to "create and implement meaningful public partnerships, ensure interagency and intra-agency coordination, and establish and implement accountability measures."[92] The Environmental Justice Strategy focuses on: (1) policy development and dissemination; (2) education and training; (3) research and data collection, analysis, and utilization; and (4) services.

8.4.5 Evaluation

Evaluation provides a way to gather data systematically to inform future partnerships, later research, and the overarching funding stream. Evaluation also allows short-term, mid-term, and long-term public health impacts on breast cancer to be anticipated and measured. Evaluation of translation, dissemination, and communication strategies should begin early in a research project.[90, 93, 94] It is important to recognize, however, that research translation, dissemination, and communication activities

must be planned throughout a project before plans for evaluating these activities can be developed.

The BCERC/BCERP COTCs are an example of a research program that included an evaluation component from project initiation.[79] The COTCs have conducted their own research on communicating and disseminating findings[79, 95] and evaluated the community-university partnerships in the BCERCs to assess the effectiveness of the translation, communication, and dissemination protocols for the program across study locations.[3] Atkin and Smith[95] found that the BCERC's communication efforts influenced advocates working to address environmental issues; breast cancer organizations, government communication specialists, and contractors working to educate the public; and biological scientists attempting to translate findings into understandable reports. The evaluation also found that advance agreements on stakeholder roles related to research design, implementation, interpretation, translation, and dissemination reduced uncertainty about expectations, roles, and responsibilities and increased participation in and authorship of publications.[80] The NIEHS PEPH program also supports the development of projects that include early planning of research communication and dissemination activities and outputs and impacts that can be evaluated along the way.[90]

8.5 Gaps, Opportunities, and Recommendations for Improving Existing Research Programs

8.5.1 Gaps and Opportunities

Gaps in Research Translation

The Committee recognizes that multiple approaches are needed to translate research into policy and practice, depending on the public health and practice settings that are targeted. A full discussion of translation research findings is beyond the scope of this report. Some information on evidence-based approaches can be found in section 8.3.1 of this chapter.

The Committee's recommendations for research on breast cancer and the environment reflect Brody and colleagues'[96] approach to prevention-oriented science. This approach recognizes the complexity of breast cancer causation and employs a "strength of the evidence" assessment of "upstream" health outcomes. A "strength of the evidence" approach considers sources of uncertainty in measurements and models, cumulative and interactive effects of multiple exposures, individual variability in susceptibility to exposures, and disparities in the distribution of exposures and health effects in different populations. This approach ascertains exposure pathways and evaluates animal and cell-based studies that suggest biologically plausible links to breast cancer. New approaches for decision making in the face of uncertainty are emerging that hold promise for navigating the science based on "weight of the evidence."[35]

> "A precautionary approach would emphasize that causal inference is not purely scientific: an ethical principle of environmental health scientists—akin to the physician's 'first do no harm' dictum—holds that they should ask themselves: 'when do we know enough to act as if something is causal?' This will depend not only on the strength of evidence but also on the availability of alternative ways of achieving the same social good and on the consequences of inaction or acting in error."[97]

The Committee acknowledges the need for protective public health measures, and most but not all members agreed to recommend implementation of a precautionary approach.[97] Kriebel identified four central components of the precautionary principle: (1) taking preventive action in the face of uncertainty, (2) shifting the burden of proof to the proponents of an activity, (3) exploring a wide range of alternatives to possibly harmful actions, and (4) increasing public participation in decision making.

The precautionary approach should be embraced *at the individual, community, state, and national levels,* with a commitment to active participation in the dialogue and investment in achieving a working

model that supports the goal of primary prevention. Investment in a robust exploration of the precautionary approach presents an opportunity to make real progress toward breast cancer prevention. For example, the European Union implemented elements of the precautionary principle with the passage of Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) in 2007, which included requirements for manufacturers to provide data to support the safety of chemicals. These types of measures are expected to reduce both safety and data gaps, help prevent diseases such as cancer that result from occupational exposures, and increase health care savings.[98] Rigorous consideration of the implications of a precautionary approach for breast cancer prevention can lead to the development of tools for efficiently and effectively translating research into meaningful human health data and protective policies.

Challenges to Research Dissemination and Communication

The slow pace of research combined with the slow pace of the publication run counter to efforts to rapidly move from science to action.[85] The time from submission of research papers to acceptance and publication averages approximately 1 year.[36] Prevailing standards for strong and credible science generally: (1) require results to be verified through replication and extension; (2) prohibit researchers from public discussion and/or presentation of findings prior to publication; and (3) require scientific findings to be published before they are considered of value for policy and practice because the publication peer-review process conveys credibility.[1, 85] Scientists on a collaborative research team rely on the peer-review process to validate their work, but the time it takes for this process may be in direct opposition to community members' desire to act on research findings or use the data to support new policies, obtain additional funding, or create innovative programs.

The relative importance of scientific rigor compared to rapid dissemination of findings will vary depending on the type of data collected. For example, surveillance and reference genomic data can and should be shared rapidly because human subjects and confidentiality considerations are minimal and there are established standards for describing and interpreting these types of data. The dissemination of other types of data requires greater caution to ensure human subjects' privacy and confidentiality. Care also must be taken regarding the type and timing of findings reported back to study participants. For example, many investigators have reported only clinically relevant findings to participants. The standards for reporting findings from environmental exposure studies, however, are rapidly evolving and, in some cases, may recommend the reporting of findings when their clinical relevance is unclear.

Research findings often are translated for and disseminated to underserved communities late in the research project, often without explicit engagement of community members. Early engagement of these communities is especially vital in research on environmental factors and breast cancer, as underserved communities often are most likely to be affected by environmental justice concerns. Participatory research approaches can help to create solutions to socioeconomic, educational, language, and cultural communication gaps that can impede the goals of well-intentioned researchers.[99]

Community-based and other participatory research processes that engage advocates have led to models in which multi-stakeholder research teams develop plans for reporting findings to participants in advance of peer review and publication.[1] In addition, processes that reduce the time from research submission to public availability are emerging—such as publishing accepted peer-reviewed research online in advance of print, open access journals, and accelerated peer review.

Community-based and other participatory research projects have their own challenges that may lead to delays in the dissemination of results. Advocates and scientists often have different funding mechanisms, professional expectations, and cultures of knowledge. These differences can create challenges in the strongest science/community research

collaborations.[99, 100] Many of these challenges could be overcome via strategies that more fully utilize effective formal and informal pathways of communication within and between agencies as well as strategies for communication involving a wider range of stakeholders. Regular evaluation of academic-community partnerships also can help to identify tensions and overcome communication gaps by collecting feedback from stakeholders that supports efforts to build trust among partners and reduce conflict.[90]

8.5.2 Recommendations

These recommendations are aimed at translating and disseminating findings to a wide audience so that study results can influence public health practice and policy, prevention activities, and medical care and inform personal choices related to breast health.

Require research projects on breast cancer and the environment to integrate research translation, dissemination, and communication plans early and throughout the research process in ways that facilitate partnerships with stakeholders from scientific, breast cancer advocacy, environmental justice, and provider communities.

Attaining prevention-based public health goals related to breast cancer and the environment requires the inclusion of translation, dissemination, and communication plans in the intramural and extramural research development process at early stages, with funding allocated for these activities. These plans should be part of the initiative-development process within federal agencies and a required component of all studies of breast cancer and the environment.[39, 75, 90, 93] Research translation, dissemination, and communication plans should consider activities, outputs (e.g., communication products), and anticipated impacts in developing a framework for integrated and ongoing evaluation of agency research translation activities.[90] Specifically, these communication plans should:

- Create a process to translate, communicate, and disseminate research findings: (1) across all HHS agencies; (2) to all agencies with regulatory jurisdiction over areas related to research on breast cancer and the environment; (3) to external networks of advocates and stakeholders who have the educational/communication tools to translate findings into breast cancer prevention actions; (4) to medical practitioners; and (5) to the wider public, using emerging and innovative communication technologies and strategies.

- Target communities affected by socioeconomic disparities, specific social stressors, racism, geographic proximity to various sources of pollution, risky occupational exposures, and deficits in the built environment that likely affect diet, physical activity, and other relevant health behaviors.

- Expand community and/or breast cancer advocate involvement in science and further develop opportunities and tools for science-advocate collaboration by establishing:

  » Formal structures for community participation and power sharing. Structures should target diverse socioeconomic, ethnic, and cultural communities.

  » Expanded programs to train advocates for inclusion in research projects, grant review, and research translation, communication, and dissemination efforts.

  » Resources that permit adequate compensation of advocates and community consultants.

  » Train programs to enhance scientists' knowledge of and need for research translation.

Translate, disseminate, and communicate research findings to stakeholders in a timely manner while targeting a wide range of disciplines, professions, and communities.

Stakeholders can serve as excellent resources for the translation, dissemination, and communication of

research. To facilitate effective translation, dissemination, and communication:

- Engage advocates, environmental justice communities, and other public stakeholders early and often.
- Create many venues, forums, and environments to encourage the sharing of perspectives and knowledge toward the common goal of breast cancer prevention.

The pace of publication of research findings is too slow—it takes, on average, 1 year from submission to publication of results.

- Support research on the best methods for reporting back the study findings to stakeholders. This research should include a review of current policies and ethical standards that might affect report back.
- Prioritize and expand the use of accelerated peer review, ahead-of-print publication, and open access journals to promote the rapid integration of new knowledge into the published body of research and timely dissemination and communication to stakeholders.
- Identify and measure criteria for effective translation, dissemination, and communication efforts, including an increase in breast cancer prevention efforts such as public health interventions, health behavior interventions, relevatnt regulatory policy decisions, and new research directions.

Use interagency and interorganizational collaborations to coordinate and amplify messages regarding what is known about the environmental causes of breast cancer.

Lack of interagency coordination and collaboration can hinder research communication and dissemination. Scientists in research-oriented agencies may not have methods to ensure that the information they generate reaches the appropriate groups in other agencies that are responsible for regulating certain exposures. Collaborative interagency programs have been applied successfully to the communication of environmental health concerns about childhood lead exposure[101] and secondhand smoke.[102] Organizations can collaborate to:

- Develop coordinated press releases and news stories.
- Create targeted social media campaigns.
- Coordinate web content.
- Disseminate quotes from scientists representing multiple agencies.
- Coordinate recommendations for public health or personal action to reduce confusion.

Identify strategies for determining when and how (i.e., at what point of evidence) to take action when breast cancer risk or survival is suspected to be associated with environmental exposures or risk factors.

To protect public health, strategies are needed for acting in the face of uncertainty or incomplete knowledge regarding environmental exposures and risk factors. These strategies should rely on the weight of the best available evidence in decision making. Translation of public messages about research findings related to environmental exposures and breast cancer has been inconsistent and delayed. Public health policy and intervention strategies are needed to expedite the communication and translation of key findings, particularly to high-risk populations. Relevant agencies should work with advocates and stakeholders to establish criteria for determining the extent of scientific evidence needed to take action to:

- Remove or reduce chemical exposures and physical agents from the environment and from commercial products/activities.
- Influence risk behaviors (e.g., tobacco controls, food labeling).

8.6 Policy Implications

Primary prevention of new breast cancer cases requires a focus on identifying and reducing exposures that increase the risk of the disease. Research translation requires that results be tied not only to personal or physician actions, but also to federal, state, and local policies that directly or indirectly create measurable changes in environmental factors linked to breast cancer incidence, morbidity, and mortality. Policies affect a wide range of system-level factors, including research funding priorities, data collection and data sharing methods, interagency collaboration and coordination, stakeholder inclusion, research translation into health behavior recommendations and clinical practice guidelines, and the advancement of regulatory efforts to proactively protect public health. The overarching goal of developing and implementing a national breast cancer prevention strategy requires sustained coordination across both research and regulatory agencies, with the clear objective of reducing or eliminating toxic environmental exposures and modifying social and lifestyle factors that are implicated in breast cancer. To this end, policies guiding the conduct, interpretation, and translation of research are needed to facilitate the advancement of regulatory policies that proactively protect public health.

> Primary prevention measures include activities that help avoid a given health care problem. Because successful primary prevention helps avoid the suffering, cost, and burden associated with disease, it is typically considered the most cost-effective form of health care.
> *—U.S. Preventive Services Task Force*

Policies affect how research is conducted. NIH policies require the inclusion of women and minority groups in clinical research, as well as the reporting of the race and ethnicity of research subjects (see http://grants.nih.gov/grants/funding/women_min/women_min.htm). Other policies that affect how research is conducted include the establishment of cancer registries, exposure monitoring, adoption of laboratory best practices, funding priorities, drug postmarketing surveillance, management of real or potential conflicts of interest or scientific misconduct, and interagency coordination to reduce duplication and increase effective leveraging of resources.

Policies affect how research is reported. NIH data sharing policies include policies for posting data from genome-wide association studies.[103, 104] These policies make data available for mining by researchers outside of the original team, which facilitates innovative research and the efficient use of funding and time expenditures. The U.S. Food and Drug Administration (FDA) has policies regarding the reporting of research from clinical trials.[105] Such policies, along with journal policies that describe how studies and their findings are to be reported, help others to evaluate or replicate the research. Institutional review boards have policies that protect the privacy of study subjects throughout the release of study data. Finally, policies can provide guidance for reporting results back to participants.

Policies affect how research results are interpreted. Interpretation of results can affect whether more research is recommended on a topic. The NTP Report on Carcinogens and the International Agency for Research on Cancer (IARC) have established criteria for evaluating the weight of the evidence for the carcinogenicity of exposures. Depending on how well the evidence meets these criteria, federal agencies may conclude that more research is needed on a given environmental risk factor in relation to breast cancer. NTP and IARC develop their criteria using the same types of evidence. This evidence is obtained from literature on environmental agents' properties, production use, human exposure, toxicokinetics, cancer studies in humans and experimental animals, and mechanisms of cancer induction and related effects. Both organizations use expert panels in developing their reports and criteria. NTP uses an extensive peer and public review process to categorize a substance as a known human carcinogen or reasonably anticipated to be a human carcinogen.[106] The IARC expert panels use the evidence to classify the agent or mixture as demonstrating

sufficient evidence of carcinogenicity (the agent/mixture is a cause of cancer), limited evidence of carcinogenicity, inadequate evidence of carcinogenicity, or evidence of no carcinogenicity.[107]

Policies can direct the inclusion of biologically plausible concerns such as cell cycle changes,[108] endocrine disruption,[108, 109] and altered mammary gland development[54, 108, 110] in assessments of the effects of agents and mixtures. In weight-of-the-evidence assessments of chemicals, policies also can ensure the use of data that link early life exposures to concerns regarding adverse health impacts[54, 111-113] in ways that inform actions by individuals, clinicians, and regulators. The navigation guide presented in Figure 8.2 provides a clear pathway for evaluating evidence and creating recommendations for action.[35]

Policies affect how the results from research on breast cancer and the environment are disseminated and translated into more effective preventive strategies and treatment. Policies are particularly important when the required preventive action cannot be implemented by personal choice or by the clinician, but must be carried out by governments or industry. For example, policies on regulation of pesticides in water supplies may be essential to translating research findings that link breast cancer with pesticide exposure into an effective prevention strategy. In addition to strengthening governmental policy on environmental exposures, policy development could focus on product suppliers. Large retailers, government agencies, and institutional groups could adopt policies that promote the development and testing of products that are free of chemicals of high concern, particularly with regard to breast cancer.

An example of how policy can affect the dissemination and translation of results relates to medical imaging procedures that rely on ionizing radiation. As a result of rapidly increasing exposures in this area (the total population's total exposure nearly doubled in the last two decades[114]), the FDA[115] called for public health approaches to medical radiation that balance the benefits of medical imaging with the risks of low- and moderate-dose ionizing radiation, including risks for breast and other cancers.[17] Suggested public health actions directed toward limiting these risks of breast cancer include: (1) active dissemination and adoption of appropriate use criteria that are developed by professional organizations to facilitate clinical decision making in medical imaging; (2) implementation of radiation tracking for patients through electronic medical records; and (3) translation and communication of the effects of medical radiation to support patient collaboration with physicians in decision making. Emerging science, which often is complex and incomplete—as in the case of low-dose medical radiation used in mammography—must be communicated effectively and in ways that acknowledge both the potential for change and unanswered questions.

Policies can guide the development and safety assessment of alternative chemical, manufacturing, and waste disposal practices. Such policies can support the public's desire for products that are free of chemicals with biologically plausible links to breast cancer and for neighborhoods and workplaces with reduced exposures to industrial emissions and hazardous waste.[98, 116] Policy is needed that supports incentives for developing safer and "greener" alternatives to chemicals of concern and chemical production in general (Safe Chemicals Act of 2011).[a] EPA's Design for the Environment[117] provides a public-private partnership model that works with businesses to choose safer technologies and alternative chemicals and provide consumers with information that helps them choose safer options. Alternatives to chemicals of concern need to undergo comprehensive screening in balance with the concerns about the chemical or chemicals in common use, and findings should be disclosed fully to the public. Green chemistry solutions shift the policy discussion from regulating specific chemicals to focusing on the best approach for meeting a specific need and function and developing safe alternatives.[118] Rather than continuing to design policy to limit, restrict, and prohibit chemical uses, new policy approaches also should reward and encourage safer and more sustainable technologies, practices, and products.

[a] Safe Chemicals Act of 2011, S. 847, 112th Congress (2011).

Policies can ensure the public's right to know about the chemicals and physical agents used in consumer products and released into the environment. Such policies can shape the public's ability to make choices that reduce exposures and to request that companies provide safer products. Policies already guide the disclosure of the ingredients and nutritional content of foods, which helps consumers make dietary choices. Analogous policies do not exist for consumer products and, as a result, the public lacks access to information about commercial products and their constituents throughout the supply chain.[15] Current protections granted to confidential business information (CBI) can hinder research and prevent the identification of true hazards. For example, research on the health effects of pesticides typically addresses only the "active ingredient" in pesticide formulations, with the composition of the "inerts" unknown to the researcher. Similarly, "fragrance" on an ingredient label does not inform the consumer that the product contains "phthalates," which are of concern in breast cancer risk. Unfortunately, "inerts" may not be inert biologically but may be composed of petroleum solvents, emulsifiers, and other compounds. In 2010, the EPA challenged industry to voluntarily declassify unwarranted CBI claims and issued new guidance outlining the Agency's plans to deny confidentiality claims for chemical identity in health and safety studies under the Toxic Substances Control Act (TSCA).[119] Knowledge gaps regarding possible effects of chemicals on the breast can be filled by requiring companies to report chemical source, use, and discharge information, as well as manufacturing volume.[120]

Policies can establish environmental justice. Lifestyle, social context, economic determinants, and disparate or unequal environmental exposures are likely to create disproportionate risks among minority and poor populations. These influences and exposures are, for the most part, modifiable and thus represent the best, targeted opportunity to reduce breast cancer disparities. Targeted research is needed to better understand the specific environmental risks for breast cancer in underserved populations. Targeted policies also are needed to ameliorate environmental disparities. These risks may include lower access to fresh, healthy foods; fewer safe places to work, play, and engage in physical activity; and disproportionate exposures to chemicals and environmental agents. Because many environmental factors interact with one another to increase risks,[17, 121] comprehensive policies to reduce the broad spectrum of exposures are needed to prevent breast cancer in certain populations and, thereby, eliminate disparities.

Policies can improve the built environment. Some populations may face significant barriers to making healthy lifestyle choices (e.g., physical activity, diet). Policies can shape features of the built environment that facilitate active lifestyles and provide access to healthy foods. For instance, local policies can increase walkability and pedestrian and bicycle safety, locate schools in areas that allows children to walk to school and that provide adequate play spaces, and create zoning and tax policies that attract grocery stores and limit fast food outlets.[122] Multiple stakeholders (including those in the agriculture, food manufacturing, retail outlet, recreation, transportation, education, real estate, and urban planning industries) need to be involved alongside community members to generate and implement solutions.[122]

Emerging research suggests that features of the built environment in low-income, African American neighborhoods can increase vigorous physical activity[123] and overall physical activity for children.[124] Further research is needed to better understand the features of the built environment that best support physical activity in different populations.[33,34,125]

Policies can improve the availability of fresh foods for communities that have inadequate access to such foods. For example, financing initiatives can create incentives for supermarkets to establish stores in food deserts,[126] although other barriers also may need to be addressed, such as perceived or real safety concerns. Federal food assistance programs, such as Supplemental Nutrition Assistance Program (SNAP, formerly food stamps) and

and Children (WIC), can influence the availability of fresh foods by providing incentives to purchase those foods.[126] These incentives, in turn, drive demand and thus encourage local retailers to stock fresh foods. An example is New York City's Health Bucks program, which offers a $2.00 bonus in SNAP benefits for every $5.00 spent at a farmers' market. This program more than doubled New York City's SNAP sales at farmers' markets, which serves the dual purpose of increasing access to fresh foods and supporting a sustainable food system. Similarly, in San Francisco, SNAP users who spend $10.00 at farmer's markets receive an additional $5.00 to spend at the market.[127] The Consolidated and Further Continuing Appropriations Act, 2012 (P.L. 112-55) provided $4,000,000 to increase the number of farmers' markets participating in SNAP, beginning in late 2011.[128]

Policies can shape the dissemination and implementation of research findings into public health programs. Sanchez and colleagues[129] presented the need for innovative strategies that support better dissemination and implementation of tested interventions that promote health behaviors. The NCI's Cancer Control P.L.A.N.E.T. (Plan, Link, Act, Network with Evidence-based Tools) is one example of an innovative tool that provides a platform for disseminating research-tested interventions to public health and clinical health providers in a single portal.[30] When P.L.A.N.E.T. was launched in 2003, the portal only provided information about physical activity and tobacco control interventions P.L.A.N.E.T. now includes information on interventions relevant to diet/nutrition, sun safety, survivorship, and public health genomics.[129] Information in P.L.A.N.E.T. is linked to interactive data from the Research-Tested Intervention Programs (RTIPs), which provides summary information about federally supported research to assess the efficacy of interventions. Studies in RTIPs are rated for the intervention impact, dissemination capacity, and other translation criteria.[31]

Policies can facilitate primary prevention of disease by reducing certain exposures. As recommended by the President's Cancer Panel in 2010, "A more integrated, coordinated, and transparent system for promulgating and enforcing environmental contaminant policy and regulations, driven by science and free of political or industry influence, must be developed to protect public health."[15] Federal agencies, including the FDA, Consumer Product Safety Commission, U.S. Department of Agriculture, Occupational Safety and Health Administration, and a number of EPA offices, independently engage in efforts to characterize and limit exposure to chemicals and radiation from a range of sources, including air, water, agriculture, industry, and consumer products. Testing, risk assessment, and regulatory guidelines vary among agencies and offices within agencies. This makes it challenging to compile all of the known information about the hazards, uses, human and environmental exposures, and regulations regarding a specific chemical or physical agent. Policies could harmonize how agencies address issues such as cumulative and aggregate exposures to chemicals that may act additively[130, 131] or synergistically[132,133] as well as windows of susceptibility, nonlinear dose-response relationships, and epigenetics. Policies also can provide standards for interpreting evidence into public health action.[35, 108, 109, 134-138]

In a 2009 report,[139] the Government Accountability Office (GAO) found that, although the TSCA authorizes the EPA to ban, limit, or regulate chemicals, the threshold to take action requires meeting a prohibitively high level of risk after conducting a lengthy and expensive cost-benefit analyses. Based on deficiencies identified in the report, the GAO added TSCA reform to its high-risk list. The EPA's own analysis led to six principles for reforming the TSCA.[140]

- Principle 1: Chemicals should be reviewed against safety standards that are based on sound science and reflect risk-based criteria protective of human health and the environment.

- Principle 2: Manufacturers should provide the EPA with the necessary information to conclude that new and existing chemicals are safe and do not endanger public health or the environment.

- Principle 3: Risk management decisions should take into account sensitive subpopulations, cost, availability of substitutes, and other relevant considerations.

- Principle 4: Manufacturers and the EPA should assess and act on priority chemicals, both existing and new, in a timely manner.

- Principle 5: Green chemistry should be encouraged, and provisions assuring transparency and public access to information should be strengthened.

- Principle 6: The EPA should be given a sustained source of funding for implementation.

These recommendations for TSCA reform warrant consideration and harmonization with the roles of other agencies in testing and managing chemicals and physical agents which, in turn, necessitates interagency coordination on policies to reduce exposures. Research currently is exploring alternative approaches for reviewing and weighing the evidence on exposures and applying the evidence to shape public health decisions.[35] Better methods to navigate science-based decision making can facilitate targeted public health interventions focused on the wide range of environmental exposures explored in this report, and inform the development of recommendations that can be disseminated and communicated to stakeholders in government and medicine, public health workers, and the public.

To summarize, policy matters in the translation, dissemination, and communication of research to prevent breast cancer. A comprehensive breast cancer prevention strategy requires the implementation of policies that protect public health and prevent breast cancer by translating and disseminating the best available evidence and providing guidance on how to act in the face of uncertainty or incomplete knowledge.

8.7 Conclusion

The efficacy and reach of interagency collaborations to study breast cancer and the environment will be improved by including research translation, dissemination, and communication plans in all intramural and extramural research activities. Resource allocation will be needed to support the development and implementation of these plans. Although many agencies have made commendable efforts to translate, disseminate, and communicate research, the need still exists for proactive interagency collaborations and increased strategic messaging across agencies to assist the public in understanding the complexities and uncertainties associated with research progress.

The cost of inaction could mean lags of a decade or more before today's research investments can be applied to preventing breast cancer. Research translation, dissemination, and communication efforts that use traditional and emerging technologies can expand and deepen the preventive public health impact of findings and lead to enduring contributions to the well-being of individuals, communities, and the Nation as a whole. This work is the responsibility of all involved parties, including the scientists engaged in the research, federal agencies that conduct and support the research, and communication partners engaged in the effort. This goal can be achieved most effectively by creating an interagency collaborative dissemination model for research on breast cancer and the environment that can be translated, disseminated, and communicated appropriately and effectively to all stakeholders.

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9
CHAPTER

The Path Forward

The Committee was charged with preparing a report that identifies advances in breast cancer research and outlines key questions, methodologies, and knowledge gaps. Another charge to the Committee was to develop a comprehensive strategy for accelerating transdisciplinary, innovative, and collaborative research on breast cancer and the environment across federal agencies and in partnership with nonfederal organizations. Further, the Committee was to identify approaches to increase public participation in decisions about breast cancer research and delineate modes of information dissemination to the community about this research. After detailed study, the Committee articulated its strong commitment to increasing the overall investment in prevention research to identify the causes of breast cancer and identify interventions. Research across the life span—*in utero*, infancy, early childhood, adolescence, reproductive years, middle age, and old age—will inform specific prevention intervention strategies to mitigate risk during sensitive windows of time when the breast is most susceptible to damage.

Taken in its entirety, this report presents a bold plan for breast cancer prevention.

The Committee integrated all of the information and conclusions from the chapters to propose a series of overarching recommendations. These recommendations, taken together, would coordinate and leverage work at individual federal agencies to provide a strategic approach to supporting and conducting future research on breast cancer and the environment. This approach would include designing a comprehensive knowledge management tool with input from scientific and advocacy communities to identify and monitor future scientific opportunities and research progress relevant to breast cancer and the environment. The strategic approach also would involve mechanisms that encourage a transdisciplinary approach and promote innovation in studies of the myriad causes of this complex disease. In addition, the approach would increase public participation in all phases of the research enterprise, drawing on the past and present contributions of breast cancer advocates. The Committee acknowledges the need for additional research on underrepresented and underserved minority groups as well as training of scientists (particularly those from populations underrepresented in the biomedical sciences) in disciplines that are involved in answering questions about breast cancer and the environment. The Committee further recognizes the need for improved and rapid communication of research findings to a diverse public.

To summarize the most important points from the many individual recommendations that were made in this report, the Committee developed seven overarching recommendations to guide progress toward understanding the role of the environment in breast cancer and, ultimately, preventing this devastating disease. These recommendations are intended to highlight priority issues for policy makers, scientists, and the public and to serve as building blocks for advancing the important work in this area begun over the past decade.

9

Overarching Recommendations

Prioritize Prevention

The Committee recommends a national breast cancer prevention strategy to prioritize and increase federal government investments in breast cancer prevention.

Historically, investments in breast cancer research have focused primarily on diagnosis and cure. Future investments must focus on prevention. Our analysis shows that the area of breast cancer prevention remains underfunded at the federal level. We must:

- Utilize a broad definition of prevention that extends beyond pharmacologic strategies directed at women who are at high risk for breast cancer.
- Conduct research in underrepresented populations to better understand health disparities.
- Recommend an examination of chemical and physical agents and other environmental factors that influence breast cancer risk.
- Recommend a shift in research priorities toward studying multiple environmental and behavioral factors jointly and developing interventions to reduce harmful exposures and promote healthy lifestyles.
- Clearly articulate the benefits of reallocating breast cancer research resources toward prevention.

Transform How Research Is Conducted

The Committee recommends investigation into compelling scientific themes using a transdisciplinary approach.

The complexity of breast cancer and the environment research requires an approach that brings many disciplines and perspectives to work together in new and creative ways. Compelling themes include: gene/environment interactions; mechanisms that underlie breast cancer subtypes; epigenetic alterations that occur over the life course, with specific exploration of normal or disease endpoints (e.g., exploring the relationship between environmental exposures and breast development, which indirectly impacts breast cancer); the impact of multiple risk factors; and periods when the breast may be most susceptible to exposures. Research also should focus on the intergenerational effects of environmental factors on breast cancer risk by employing the animal-to-human paradigm. An animal-to-human paradigm involves conducting (1) studies of animal models to generate hypotheses for human studies and to aid in the interpretation of the findings from human research and (2) human studies that may generate additional questions that can be tested under controlled conditions with animal models. Finally, research is needed to better understand the varying exposures and risk profiles among all racial and ethnic populations, especially those that are understudied. Scientific progress in all of these areas will require funding initiatives that encourage grant proposals from multiple lead investigators representing a diversity of relevant disciplines, as well as stakeholder involvement.

To speed the research process, it will be necessary to fully utilize high throughput technologies that are capable of evaluating multiple potential risk factors simultaneously, having streamlined study protocols that can move the study of particular risk factors and environmental agents through a research pipeline that will enable scientists to quickly understand the potential of factor to cause breast cancer and conduct the necessary studies to confirm it, having funding mechanisms and research resources available that can be rapidly deployed to address emerging issues related to breast cancer and the environment. Excellent examples exist, but could be enhanced and more fully deployed.

Intensify the Study of Chemical and Physical Factors

The Committee recommends research on the effects of chemical and physical factors that potentially influence the risk of developing and the likelihood of surviving breast cancer.

Filling the knowledge gaps regarding how environmental exposures affect mammary glands in animals and human breasts requires a comprehensive approach that includes *in vivo*, *in vitro*, and human studies. It is critical that agencies develop and apply standards for testing chemical and physical effects, obtain public input on high-priority agents, and make findings immediately available. We must:

- Develop and apply techniques, including biomonitoring, that measure levels and response to mixtures of exposures relevant to breast cancer with the greatest possible precision.

- Regularly monitor levels of environmental exposures and biospecimens collected from diverse populations. Prioritize chemicals that are produced in high volumes with biologically plausible evidence of their role in the development of breast cancer. Attention should be paid to different exposure concentrations of physical and chemical agents. It is important to recognize that low level exposures can be a concern in susceptible populations, at specific periods in the life course, in combination with other risk factors, or for other reasons.

- Conduct, coordinate, and integrate studies across federal agencies and develop standards that consider the full scope of evidence from *in silica*, *in vitro*, *in vivo*, and epidemiologic studies regarding health risks and safety to the extent possible.

- Rapidly communicate results of the research on these chemical and physical agents so that they can be used to inform policy.

Plan Strategically Across Federal Agencies

The Committee recommends that federal, state, and nongovernmental organizations coordinate and collaborate to accelerate the pace of scientific research on breast cancer and the environment.

Joint planning and better coordination of the efforts of both governmental and nonfederal funders would increase the visibility of research on breast cancer and the environment, promote the goal of breast cancer prevention, facilitate sharing of resources, help to identify the most critical scientific questions in this area, and monitor progress toward answering these questions. In implementing a federal breast cancer and the environment research strategy, the Committee sees the need for comprehensive research tools to help conceptualize and guide the planning and prioritization of future federal programs, as well as efforts to expand trans-agency programs such as the NIH Common Fund, interagency collaborations, and public-private partnerships. To promote collaboration across agencies and partner organizations that advance understanding of breast cancer and the environment, we must:

- Conduct regular and frequent forums to discuss key opportunities and resources for breast cancer prevention research.

- Develop opportunities for joint strategic planning and coordination of research initiatives.

- Monitor progress using sound metrics of success and communicate that progress to the public regularly.

- Encourage participation from the full range of stakeholders, including the public, policy makers, and public health and clinical practitioners, in the development and implementation of federal agency research plans relevant to breast cancer and the environment.

- Develop knowledge integration tools, databases, or flow charts (also referred to as "frameworks") to assist with strategic planning by monitoring improvements in knowledge and facilitating the communication of research progress to various stakeholders. These knowledge integration tools will help users to understand and organize complex factors, relationships, and processes involved in the study of breast cancer and the environment.

Engage Public Stakeholders

The Committee recommends that the research planning, implementation, and translation process include stakeholders who represent the public and affected communities at every stage.

Public representatives should be involved as equity members in the design and implementation of research programs, in the translation of research findings into public health and regulatory actions, and in communicating research and intervention needs to a diverse public. Specifically, we should:

- Train and prepare stakeholders to fully participate across the research enterprise.

- Financially compensate stakeholders for their time, effort, and expertise while they participate in the research process.

Train Transdisciplinary Researchers

The Committee recommends federal programs that encourage and enable scientists to engage in transdisciplinary research.

Accelerating research on breast cancer and the environment will require increasing the numbers of large, transdisciplinary activities. Scientists from many disciplines must be engaged to develop new ways of thinking about breast cancer prevention. Scientists require training across the career trajectory—from undergraduate to investigator—to develop the skill sets necessary for active and effective engagement in transdisciplinary research. Opportunities and incentives for acquiring these skills are needed to promote involvement. Specifically, we must:

- Support training programs that promote transdisciplinary skill sets for all partners.

- Investigate ways to reward and promote scientists who work on transdisciplinary teams.

Translate and Communicate Science to Society

The Committee recommends that the translation and dissemination of research findings be built from the start into every funded program that focuses on breast cancer and the environment.

Findings generated by research on breast cancer and the environment must be communicated and, when appropriate, translated into interventions. These findings must be communicated to multiple audiences expeditiously and in ways that allow for the information to be easily used for prevention, policy, clinical, and educational efforts. Specifically, we must:

- Bring together the assets of all federal agencies to utilize dissemination models that provide a current stream of information on breast cancer and the environment.

- Mandate that research projects on breast cancer and the environment integrate research translation, dissemination, and communication plans throughout the research process in ways that facilitate partnerships with stakeholders from the scientific, advocacy, and practitioner communities, among others.

- Train researchers, advocates, and other stakeholders in communication techniques that will facilitate the flow of research findings to the public.

- Evaluate whether research recommendations are being implemented and translated into public health and clinical practice.

Research on the complex causes of breast cancer has been a daunting task. Over the past decades there have been some important and meaningful advances, and much progress has been made in understanding the basic mechanisms of mammary carcinogenesis, detection of the disease, and its treatment. Many lives have been saved when diagnoses were made early and targeted treatments were successful. The Committee, however, is committed to making the prevention of breast cancer a priority. Identifying the multiple causes of breast cancer, reducing exposure to these causes, and intervening during different time points across the life span is the work of prevention-oriented research and dissemination programs. These programs also must integrate existing evidence across a wide range of disciplines to create a clear picture of how environmental and genetic factors interact to initiate and promote breast cancer. This evidence must be moved out of the "laboratory" and into the field quickly and transparently to inform and educate all stakeholders, including the general public, about risks and ways to prevent breast cancer. Rapid dissemination of information will allow individuals to identify prevention strategies for themselves, their families, and their communities. Prevention strategies may involve lifestyle modifications, such as changes toward a healthy diet, fighting obesity, and/or increasing physical activity; making smart choices about consumer products; or protecting oneself and others from chemicals linked to breast cancer in the workplace and at home. Prevention strategies also may include policy development and implementation at the local, state, and national level to reduce environmental risks and promote healthy lifestyles. Public-private partnerships must be leveraged to ensure that these prevention strategies are integrated into public health programs at the federal, state, and community levels. Working together in new ways that bring committed scientists, advocates, and many stakeholders together will move us on the path toward a world without breast cancer.

Appendices

Appendix 1. Interagency Breast Cancer and Environmental Research Coordinating Committee Charter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, N.C. 27709
Website: www.niehs.nih.gov

CHARTER
INTERAGENCY BREAST CANCER AND ENVIRONMENTAL RESEARCH
COORDINATING COMMITTEE

AUTHORITY

Public Health Service Act (PHSA) section 417F, 42 U.S.C. 285a-12, as amended. The Interagency Breast Cancer and Environmental Research Coordinating Committee (Committee) is governed by the provisions of the Federal Advisory Committee Act, as amended (5 U.S.C App.), which sets forth standards for the formation and use of advisory committees.

OBJECTIVES AND SCOPE OF ACTIVITIES

The Committee will review existing research activities within the Department of Health and Human Services (DHHS) and other Federal agencies concerning breast cancer, particularly research being conducted on environmental and genetic factors that may be related to the etiology of breast cancer. Upon review of these research activities, the Committee will develop a summary of advances and make recommendations to the Secretary DHHS (Secretary) regarding research gaps and needs. The Committee also will serve as a forum and assist in increasing public understanding of the member agencies' activities, programs, policies, and research, and in bringing important matters of interest forward for discussion.

DESCRIPTION OF DUTIES

As specified in PHSA section 417F(a)(2), the Committee will (1) share and coordinate information on existing research activities, and make recommendations to the National Institutes of Health (NIH) and other Federal agencies regarding how to improve existing research programs, that are related to breast cancer research; (2) develop a comprehensive strategy and advise the NIH and other Federal agencies in the solicitation of proposals for collaborative, multidisciplinary research, including proposals to evaluate environmental and genomic factors that may be related to the etiology of breast cancer that would (a) result in innovative approaches to study emerging scientific opportunities or eliminate knowledge gaps in research to improve the research portfolio, (b) outline key research questions, methodologies, and knowledge gaps, (c) expand the number of research proposals that involve collaboration between 2 or more national research institutes or national centers, including proposals for Common Fund research described in PHSA section 402(b)(7) to improve the research portfolio, and (d) expand the number of collaborative, multi-disciplinary, and multi-institutional research grants; (3) develop a summary of advances in breast cancer research supported or conducted by Federal agencies relevant to the diagnosis, prevention, and treatment of cancer and other diseases and disorders; and (4) not later than 2 years after

the date of the establishment of the Committee, make recommendations to the Secretary of the (DHHS) (i) regarding any appropriate changes to research activities, including recommendations to improve the research portfolio of the NIH to ensure that scientifically-based strategic planning is implemented in support of research priorities that impact breast cancer research activities, (ii) to ensure that the activities of the NIH and other Federal agencies, including the Department of Defense, are free of unnecessary duplication of effort, (iii) regarding public participation in decisions relating to breast cancer research to increase the involvement of patient advocacy and community organizations representing a broad geographical area, (iv) on how best to disseminate information on breast cancer research progress, and (v) on how to expand partnerships between public entities, including Federal agencies, and private entities to expand collaborative, cross-cutting research.

AGENCY OR OFFICIAL TO WHOM THE COMMITTEE REPORTS

The Committee reports to the Director, National Institute of Environmental Health Sciences (NIEHS).

SUPPORT

Management and support services will be provided by the Division of Extramural Research & Training, NIEHS.

ESTIMATED ANNUAL OPERATING COST AND STAFF YEARS

The estimated annual cost for operating the Committee, including compensation and travel expenses for members, but excluding staff support is $78,955. The estimated annual person years of staff support required are 1.0, at an estimated annual cost of $104,691.

DESIGNATED FEDERAL OFFICER

The Director, NIEHS, will assign a full-time or permanent part-time NIEHS employee as the Designated Federal Officer (DFO) of the Committee. In the event that the DFO cannot fulfill the assigned duties of the Committee, one or more full-time or permanent part-time NIEHS or NIH employees will be assigned these duties on a temporary basis.

The DFO will approve or call all of the Committee's and subcommittees' meetings, prepare and approve all meeting agendas, attend all Committee and subcommittee meetings, adjourn any meeting when it is determined to be in the public interest, and chair meetings when directed to do so by the Director, NIEHS.

ESTIMATED NUMBER AND FREQUENCY OF MEETINGS

Meetings of the full Committee will be held not less than one time within a fiscal year. Meetings will be open to the public except as determined otherwise by the Secretary of DHHS in accordance with subsection (c) of section 552b of Title 5 U.S.C. Notice of all meetings will be given to the public. In the event a portion of a meeting is closed to the public, as determined by the Secretary in accordance with the Government in the Sunshine Act (5 U.S.C. 552b(c)) and the Federal Advisory Committee Act, a report will be prepared which will contain, as a minimum, a list of members and their business addresses, the Committee's functions, dates and places of meetings, and a summary of the Committee's

activities and recommendations made during the fiscal year. A copy of the report shall be provided to the Department Committee Management Officer.

DURATION

Continuing. This Committee is mandated with no specified end date. The Director, NIEHS, will review the necessity of the Committee in calendar year 2013 and, thereafter, at least once every 2 years.

TERMINATION

Unless renewed by appropriate action prior to its expiration, the Charter for the Interagency Breast Cancer and Environmental Research Coordinating Committee will expire two years from the date the charter is filed.

MEMBERSHIP AND DESIGNATION

The authority to appoint the members of the Committee has been delegated to the Director, NIEHS.

The Committee will be composed of not more than seven voting Federal representatives, to include the following representatives, or their authorized designees:

- the Director of the Centers for Disease Control and Prevention;
- the Director of the NIH, and the directors of such national research institutes of the NIH as the Director, NIEHS, determines appropriate;
- One representative from the National Cancer Institute Board of Scientific Advisors, appointed by the Director of the National Cancer Institute;
- the heads of such other agencies of DHHS as the Director, NIEHS, determines appropriate; and
- representatives of other Federal agencies that conduct and support cancer research, including the Department of Defense.

The Committee will include twelve additional voting members appointed by the Director, NIEHS, to include the following:

- Six members appointed from among scientists, physicians, and other health professionals, who are not officers or employees of the United States; represent multiple disciplines, including clinical, basic, and public health sciences; represent different geographical regions of the United States; are from practice settings, academia, or other research settings; and are experienced in scientific peer review process.
- Six members appointed from members of the general public, who represent individuals with breast cancer.

The Committee will include such nonvoting members as the Director, NIEHS, determines to be appropriate. The voting members of the Committee will select a Chair from among such members. The selection of a Chair will be subject to the approval of the Director, NIEHS.

All non-Federal members serve as Special Government Employees. Members and the Chair shall be invited to serve for overlapping four-year terms. A quorum for the conduct of business by the full Committee shall consist of a majority of currently appointed members.

SUBCOMMITTEES

As necessary, subcommittees and ad hoc working groups may be established by the DFO within the Committee's jurisdiction. The advice/recommendations of a subcommittee/ working group must be deliberated by the parent advisory committee. A subcommittee may not report directly to a Federal official unless there is statutory authority to do so.

Subcommittee membership may be drawn in whole or in part from the parent advisory committee. All subcommittee members may vote on subcommittee actions and all subcommittee members count towards the quorum for a subcommittee meeting. Ad hoc consultants do not count towards the quorum and may not vote. A quorum for a subcommittee will be three members. The Department Committee Management Officer will be notified upon establishment of each standing subcommittee and will be provided information on its name, membership, function, and estimated frequency of meetings.

RECORDKEEPING

Meetings of the Committee and its subcommittees will be conducted according to the Federal Advisory Committee Act, other applicable laws and Departmental policies. Committee and subcommittee records will be handled in accordance with General Records Schedule 26, Item 2 or other approved agency records disposition schedule. These records will be available for public inspection and copying, subject to the Freedom of Information Act, 5 U.S.C. 552.

FILING DATE

September 25, 2011

APPROVED

APPROVED

8/15/11
Date

Linda S. Birnbaum
Director, NIEHS

Appendix 2. Endocrine Disrupting Compounds (EDCs)[a]

Bisphenol A (BPA)

BPA, a component of polycarbonate plastics and epoxy resins, is produced at high volumes and has widespread human exposure. BPA is measureable in human urine, serum, milk, maternal and fetal plasma, amniotic fluid, and placental tissues. BPA leaches into foods from the linings of food cans, baby bottles, and drink containers and may be present in dental sealants, thermal paper, and other composites. BPA also is produced in a halogenated (brominated or chlorinated) form for use as a flame retardant known as tetrabromobisphenol A (TBBPA).[1] A study in Norway found that serum levels of brominated flame retardants were increasing in humans of all ages, and that levels were markedly higher in infants and children relative to adults.[2]

Animal studies have found that exposure to BPA resulted in enhanced susceptibility of the mammary gland to chemical carcinogen challenge in rats and the development of "beaded" ducts in 9-month-old mice.[3, 4] Ductal beading (intraductal hyperplasia) is evident when actively proliferating luminal epithelial cells form a bridge across duct walls. Epithelial cells in beaded ducts have proliferative indices that are much higher than those of normal ducts. This hyperplastic event is believed to be a precursor to ductal carcinoma, suggesting that BPA induces not only an elevated susceptibility to carcinogens,[5] but also the ability to induce spontaneous tumor development. It is important to note that these effects do not require life-long exposure. Exposure during the fetal and nursing stages of life is sufficient.

Humans are constantly exposed to BPA in their diet and elsewhere. Although early life exposure to BPA has been linked to tumor development in animal studies, no human study has examined BPA exposure in early life and adult breast cancer risk. The Breast Cancer and the Environment Research Program and National Children's Study cohorts, however, offer opportunities to study early BPA exposure and breast cancer risk if their cohorts are monitored continually into adulthood.

Nonylphenol

This substance, found in the lining of food containers and wraps, cleaning compounds, and spermicides, is known for its estrogenic properties. Studies of rats found that nonylphenol produced a dose-dependent increase in mammary cell proliferation[6] and DNA mutations and chromosomal abnormalities[7] that can lead to genetic instability and an increased risk of developing neoplastic lesions and mammary tumors. Prenatal nonylphenol exposure in female rats also resulted in offspring with increased proliferative mammary epithelial branching and budding just after birth and extensive alveolar buds and increased terminal end bud (TEB) differentiation at the time of puberty.[8] These findings from animal studies suggest that this chemical has a substantial effect on mammary development following early life exposures. Although humans are exposed to this compound on a regular basis, its effects on tumor development in humans have not been evaluated.

[a] Considerable information on pesticides is included in this section because much work has occurred in this area. The U.S. Environmental Protection Agency has helped to accelerate knowledge in this area by requiring testing of all pesticides before they are marketed.

Phthalates

Di (n-butyl) phthalate (DBP) is used to soften plastics and disperse or retain scent in health and beauty products. This chemical also is found in medical tubing and children's toys. Environmental contamination by DBP and other phthalates is widespread and has been monitored in human infants following critical care procedures. A study of rats found that perinatal DBP exposure from late pregnancy until weaning resulted in abnormal mammary alveolar branching and hypoplasia in female offspring. Male offspring exposed to high doses of DBP exhibited retained nipples (normally absent) in adolescence as well as dilation of mammary alveolar buds and ducts in adulthood.[9]

N-Butyl benzyl phthalate (BBP) has been investigated by Breast Cancer and the Environment Research Centers investigators. Pre- and neonatal exposure to BBP increased the proliferative index in TEBs of 35-day-old female rat offspring. BBP also altered the genomic profile of the mammary gland of 21-day-old rats.[10] Certain members of this class of compounds currently are under health effects investigation within the Division of the National Toxicology Program. Numerous studies also have evaluated human populations for the health effects of phthalates, especially reproductive effects. Only one study, however, reported the effects of phthalates on breast cancer risk.[11] This study demonstrated a 2.2-fold increase in breast cancer risk associated with the highest quartile of urinary mono-ethyl phthalate measured levels (versus the lowest measured levels) in women of Northern Mexico. When premenopausal breast cancer risk was evaluated separately, the increase in risk was 4.13. The urinary phthalate concentrations found in this study were within the wide range found in U.S. women. The findings of the study by Lopez-Carrilo and colleagues need to be replicated in other populations.

Cadmium

Cadmium, like other naturally occurring metals, is classified as an EDC because it mimics or perturbs the normal hormonal milieu. Cadmium can alter mammary development in mice and rats, with low levels of prenatal exposure mimicking estrogen.[12] Treatment of a human breast cancer cell line (MCF-7 cells) with cadmium decreased estrogen receptor protein and mRNA, stimulated the estrogen response element, and induced cell growth. These results suggest that cadmium can modulate and promote the growth of breast cancer cells.[13] In a study of 190 premenopausal women, urinary cadmium levels were associated with a Breast Imaging-Reporting and Data Systems (BI-RADS®) density category of "extremely dense" (OR: 1.75, 95% CI: 1.14–2.70).[14] The strongest associations were noted in nulliparous women and those who had smoked (another source of cadmium exposure).

Organochlorines

Organochlorines are persistent environmental contaminants and include polychlorinated biphenyls (PCBs), chlorinated dioxins and furans, and a large number of pesticides. Many but not all organochlorines are highly lipophilic and have been detected in human breast milk and adipose tissue.[15, 16] Organochlorines are known for their estrogenic actions but also may exhibit anti-estrogenic or anti-androgenic activities.

a. **Dichlorodiphenyltrichloroethane (DDT).** DDT is an insecticide used to control insect-borne disease. It reached peak use in the United States in 1959. DDT was banned by the U.S. Environmental Protection Agency (EPA) in 1972.[17] DDT is a complex mixture of several DDT congeners, the most estrogenic being o,p′-DDT (about 15–23% of the mixture). The main congener, p,p′-DDT, forms about 77 percent of the mixture and degrades to p,p′-DDE, the most prevalent and persistent metabolite in the environment and in people; p,p′-DDE has anti-androgenic and little estrogenic activity.[18] The isoforms of DDT vary in their ability to affect the breast. o,p´-DDT can support the growth of estrogen-dependent breast tumors in rats, whereas metabolites of DDT that do not bind to the ER are without effect. There is limited evidence that DDT may act as a promoter of mammary tumors in rats.[17]

   Several nested case-control studies conducted since 1996 have failed to observe a significant positive relationship between serum or adipose tissue levels of DDE or DDT and breast cancer risk. A pooled analysis of five case-control studies from the Northeast United States (1,400 cases; 1,642 controls) demonstrated no association between breast cancer risk and p,p′-DDE.[19] A meta-analysis of 22 studies also revealed no association.[20] Consistent with this finding, countries with more recent DDT use have not found a relationship to breast cancer risk.[17] Studies in Colombia, South America,[21] and in Mexico City,[22] however, demonstrated an elevated risk of breast cancer in women with higher serum levels of DDE. Importantly, Cohn and colleagues[23] reported a significant 5-fold rise in risk of breast cancer among women exposed to p,p′-DDT prior to age 14 years, which suggests that early life exposures may be more relevant for breast cancer etiology. Overall, there is no epidemiologic evidence to support a clear association between DDE and breast cancer risk, but further research in breast cancer risk associated with DDT exposure is warranted, especially among sensitive subpopulations and considering exposures during biologically relevant time periods.

b. **Dieldrin.** Dieldrin is an agricultural pesticide that was used in the United States from the 1950s to the mid-1970s to deter soil insects and termites. Its use was banned by the U.S. EPA in 1987. Using serum samples obtained from nearly 8,000 Danish women between 1976 and 1978 and linked to breast cancer diagnoses by 1997, a significant increase in breast cancer risk was associated with serum dieldrin. Women in the highest quartile had double the risk of breast cancer compared to women in the lowest quartile (OR 2.25, 95% CI 1.32–3.84, p trend = 0.003). When the analysis was performed using an average of the blood dieldrin levels from the two collections, there was an increased risk of dying in women from the highest compared to the lowest quartile (RR: 5.76, 95% CI: 1.86–17.92, p trend < 0.01). Relative risks remained unchanged (OR: 2.05, 95% CI: 1.17–3.57, p trend = 0.01) when adjusted for confounding factors (number of full-term pregnancies and weight).

c. **Polychlorinated biphenyls (PCBs).** PCBs are another class of organochlorines that are a mixed set of isomers with varying modes of action—some being estrogenic and others demonstrating androgenic activity. Cohort studies of women with breast cancer generally have relied on stored serum PCB measurements and have not shown significant, positive associations.[17] Two cohort studies suggested possible associations between PCB exposure and breast cancer risk.[24-26] In the study by Dorgan and colleagues,[24] there was a positive association between breast cancer and exposure levels among women monitored less than 3 years before breast cancer diagnosis. Reports by Hoyer and colleagues[25, 26] showed significant associations between breast

cancer and average serum levels of total PCBs, PCB-118, and PCB-138 using blood samples that were collected twice, 5 years apart. Further, an extension of this study revealed a 3-fold increase in risk of breast cancer associated with total serum PCB levels among a subgroup with mutant p53 breast cancers.[26] The effects of PCBs on tumorigenesis in animal models have been inconsistent. This class of chemicals, however, is known to affect pubertal end points in both human girls and rodent models.[27]

d. Atrazine (ATR). ATR has undergone risk assessment since the late 1990s because of its toxicity in rodents and ability to permeate waterways, soil, and drinking water supplies. ATR still is one of the most heavily used herbicides on food and grain crops in the United States. Its use is banned in the European Union. ATR-exposed rats, especially those exposed during both pregnancy and nursing, exhibited delayed mammary gland development just after birth and extending into adulthood. ATR-exposed animals retained TEBs longer than controls, suggesting an extension of the time needed for mature mammary tissue development. These observations required only a 3-day exposure of ATR during the critical period of fetal mammary bud outgrowth.[28] Similar effects were seen when rats were exposed prenatally to a chlorotriazine metabolite mixture at concentrations 10–1,000 times lower than that of ATR in previous studies.[29] These low ATR exposure levels did not affect other pubertal end points, which suggest that mammary development and other pubertal measures are regulated by different mechanisms. The effects of ATR on estrous cyclicity and luteinizing hormone surge are regulated via the hypothalamus,[30] and mechanisms of ATR action on mammary tissue are unclear.[31] Two recent studies using different evaluation techniques[32] or a rat strain known to be less sensitive to the effects of ATR, found little effect of the herbicide on mammary end points.[33]

ATR also is known to interfere with lactational function in rats.[28] Sprague-Dawley rats fed ATR in their diet during adult life also exhibited early onset of mammary tumors and an increased incidence of those tumors.[34] The latter results support the hypothesis that exposure to ATR causes acceleration of endocrine-changing effects that result in an earlier onset of tumorigenesis, although the mechanism of action for those changes remains to be proven.[35] In addition, laboratory studies by Fukamachi and colleagues[36] and Ueda and colleagues[37] highlight a potential proliferation effect of ATR on existing tumors.

Prolonged exposure to ATR in humans, especially through contaminated drinking water, remains a concern remains for the development of breast cancer. Human studies on ATR-related breast cancer risk have had limited scope and have not addressed life stage-specific exposures. In an ecological study by Kettles and colleagues,[38] county breast cancer incidence rates in Kentucky were calculated for the years 1991to 1994 and the triazine exposure status of each county was categorized based on the water contamination (1991–1994), historical acres of corn planted in 1970, and pesticide use in 1970. Approximately 1.9 million women in the 120 counties were covered by the study. Detected triazines in surface water were positively associated with a significantly increased risk of breast cancer for low-exposed counties (OR: 1.10) and high-exposed counties (OR: 1.18) for the years 1991–1992. Low levels of groundwater contamination also were associated with significantly increased breast cancer incidence (OR: 1.17). In 1993 to 1994, low (OR: 1.10), medium (OR: 1.15), and high (OR: 1.10) groundwater contamination was associated with significantly increased breast cancer incidence. No association between surface water contamination and breast cancer incidence was found. It is unknown whether the women drank the water in which triazines were detected. Only one study[39] looked at confounders, but the women may

have been misclassified with regard to estimated ATR exposure. Other studies that used similar ecologic methods in Kentucky and the United Kingdom[40, 41] produced no significant associations.

A slightly different approach was taken by McElroy and colleagues,[39] who designed a case-control study to evaluate breast cancer risk in women drinking ATR-contaminated well water in Wisconsin. Among 6,944 women, ages 20–79 (n = 3,275 cases, n = 3,699 controls), living in rural areas and receiving water from wells, breast cancer cases (diagnosed 1988–2001) were examined relative to ATR concentrations from random well samples collected in 1994, 1996, and 2001. No association was found between breast cancer diagnosis and exposure to ATR-contaminated well water.

Overall, there has been little agreement among rodent and human studies on the effects of ATR on breast cancer risk. Ecologic studies lack controls and measures of exposure in individuals and are limited by temporal ambiguity (timing of exposure and outcome) and failure to adjust for potential confounding factors. In animal studies, differences in rat strain, evaluation methods, and study design have led to equivocal results. Additional direct comparisons are needed to determine the significance of the original findings, especially with respect to the low-dose mixture studies. Better studies must be conducted to clarify whether a relationship exists between chlorotriazine metabolites and breast cancer risk. Early life and lifetime estimates of exposure to these metabolites in conjunction with ongoing health monitoring within the Agricultural Health Study and CHAMACOS (an NIH-funded longitudinal birth cohort study examining chemicals and other factors in the environment and children's health) could provide accurate data if participants are monitored over their life course.

e. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). This industrial incineration and chemical reaction-dependent pollutant is an endocrine disruptor that binds the Aryl hydrocarbon receptor (AhR) to induce adverse effects in development and reproduction, including in the mammary glands. The carcinogenic potential of TCDD (dioxin) has been reviewed.[42]

The effect of TCDD exposure on mammary development in the rat has been studied extensively. The female offspring of three different rat strains exhibited severe and persistent mammary gland developmental abnormalities when exposed to a single dose of this lipophilic compound 1 week before birth. Adverse effects included decreased ductal branching, delayed epithelial migration into the fat pad, and fewer differentiated TEBs. Data suggest that these effects are regulated by signals from the stromal component of the gland.[43, 44] Two human studies that evaluated early life exposures to dioxins/PCBs found delayed breast development in adolescents with the highest circulating dioxin levels (Seveso, Italy)[45] or prenatal/lactational dioxin levels (The Netherlands).[46] Later life adverse effects, however, could not be determined. More recently, a 23-year mortality follow-up study of nearly 400 women employed in a Hamburg, Germany pesticide plant in which they were exposed to dioxin, found a significant increase in breast cancer mortality (standardized mortality ratio: 1.86, 95% CI: 1.12 – 2.91).[47]

Prenatal TCDD treatment of rats followed with a carcinogen challenge in early adulthood doubled the incidence of mammary tumors and decreased tumor latency compared to controls. These results suggest that TCDD causes permanent changes in the mammary glands during gestation, which results in a heightened

risk for tumors later in life.[48] TCDD also impairs normal lactation in mice exposed during rapid mammary changes in pregnancy,[49] leading to malnutrition and death in offspring.

An epidemiologic study conducted in Seveso, Italy correlated TCDD exposure following an industrial accident with an increased risk of breast cancer.[50] The hazard ratio for breast cancer associated with a 10-fold increase in serum TCDD levels was 2.1 (95% CI: 1.0–4.6). At that time, women in the study with the greatest TCDD exposure were not yet between the ages of 40 and 58, the age of highest breast cancer risk. A recent follow-up (conducted in 2008), found that individual serum TCDD measurements were significantly positively related to overall cancer incidence among the women. There also was a nonsignificant increase in the hazard ratio (HR: 1.44; 95% CI: 0.89–2.33) associated with a 10-fold increase in serum TCDD during the approximately 30-year follow-up period.[51] Because this cohort of women were young when exposed to TCDD (between 0–40 years old), some of them still have not reached menopause. They should be re-evaluated in the future.

Polybrominated Diphenyl Ether (PBDE)

Brominated chemicals are used widely for commercial and industrial products, including flame retardants in textiles, construction materials, and polymers used in electronics. This class of chemicals is known to sequester in adipose tissue and is consistently reported in breast milk. In rat dams treated from early pregnancy through weaning with a PBDE mixture (DE-71), which provides both gestational and lactational exposure, mammary gland development in high-dose female offspring was delayed, with decreased epithelial growth, limited TEB development, and decreased lateral branches just prior to puberty.[52] These findings are consistent with other findings from other studies demonstrating altered reproductive end points in rodents exposed to PBDEs.[53] Effects of exposures during puberty and tumor induction have not been assessed.

Perfluorooctanoic Acid (PFOA)

PFOA is a long half-life chemical (2–4 yrs.) used in fire-fighting foams, electronics, and to make products that are grease- and waterproof. It is the final degradation product of other > 8-carbon perfluorinated materials. PFOA is found in the serum of humans and wildlife, making it an important target for developmental toxicity studies. This chemical attaches to proteins in the blood and is reported in the breast milk of women and rodents. Studies in mice have revealed stunted mammary development after low-dose gestational PFOA exposure and persistent effects such as increased stromal density and epithelial hyperplasia.[54, 55] Mechanisms for these effects are undetermined.[54] Peripubertal exposure of mice to PFOA has been shown to inhibit mammary gland development by altering ovarian function and decreasing estrogen-dependent actions required for pubertal mammary gland development.[56] The lowest doses of PFOA that have been tested produced blood levels in mice that overlap with those reported in humans living in PFOA-contaminated communities in Ohio and West Virginia.[55] An expert panel found that delayed puberty in girls in this cohort was associated with the highest levels of serum PFOA.[57] In a British cohort, however, prenatal exposure to PFOA and other related compounds was not associated with age at menarche.[58] These two studies assessed pubertal outcomes but did not evaluate timing of breast development. A recent report[59] demonstrated, for the first time, a significant risk of breast cancer in Greenlandic Inuit women with the highest levels of perfluorinated chemicals in their blood. This case-control study was underpowered and should be repeated.

Appendix 3. Environmental Chemical Carcinogens

Polycyclic Aromatic Hydrocarbons (PAHs)

PAHs are formed as a result of incomplete combustion of hydrocarbons and have been shown to induce mammary tumors in laboratory rats.[60] Treatment of human mammary epithelial cells (HMECs) with benzo[a]pyrene initiated a genetic alteration profile similar to that induced when these cells were treated with estradiol (E2).[61] In response to treatment with the ultimate carcinogen, BDPE, HMECs showed increased DNA damage in a dose-response manner.[62] Biotransformation *in vivo* of PAHs is initiated by the CYP450 family of enzymes, particularly CYP1A1 and 1B1. Phase II enzymes such as glutathione S-transferases (GSTs), epoxide hydrolases, sulfotransferases (SULTs), and UDP-glucuronosyltransferases (UGTs) further metabolize these compounds.[63] In the Long Island Breast Cancer Study Project (LIBCSP), a population-based case-control study with the aim of identifying environmental carcinogens potentially associated with breast cancer, the presence of PAH-DNA adducts was associated with breast cancer risk.[64] The relationship did not show dose-response, however, and the odds of developing breast cancer were not significantly higher among women with the highest levels of PAH-DNA adducts detected in the blood. This finding suggests a potential threshold effect for PAH exposure and/or differential host susceptibility to the carcinogen.[65, 66] The nucleotide excision repair (NER) pathway is thought to be responsible for the removal of PAH-DNA adducts, and it is plausible that polymorphisms in the NER pathway, leading to decreased capacity for repair, could modify the risk of breast cancer among susceptible subgroups of women. Polymorphisms in the ERCC2 (XPD) gene associated with suboptimal DNA-repair capacity have been associated with an increased risk for breast cancer.[67, 68] Thus, associations between PAHs and breast cancer risk could be restricted to subgroups of women with high-risk genotypes.

Aryl Aromatic Amines

The role of aryl aromatic amines in carcinogenesis has been suspected since the 19th century, when an association was observed between exposure in aniline dye workers and bladder cancer.[69] Women may be exposed to aromatic amines from mainstream and sidestream tobacco smoke, synthetic fuels, or as the result of metabolic reduction of polycyclic nitroaromatic hydrocarbons, which are ubiquitous in diesel exhaust and airborne particulates.[70] Experimental evidence indicates that some aromatic amines, such as 4-aminobiphenyl and 4-naphthylamine, are potentially mutagenic and carcinogenic to human breast cells.

In vivo, activated aromatic amine metabolites have been shown to cause DNA damage in rodents,[71] to transform mouse mammary glands,[72] and to induce rodent mammary tumors.[73] Amines and nitroaromatic hydrocarbons demonstrate organotropism, and mammary tissue in female rats is a target for several such compounds. Certain dinitropyrenes that are found in diesel exhaust also have been shown to target the mammary gland in rodent carcinogenicity studies.[74]

In vitro, aromatic amines form DNA adducts in cultured human mammary epithelial cells[75] and cause unscheduled DNA synthesis.[76] This finding indicates that breast epithelial cells have the capacity to bioactivate these compounds. Human breast tissue also has been shown to possess N-acetyltransferase (NAT)1 activity, but not NAT2, indicating one pathway for the activation of aromatic amines.[77] In human studies, examination

of exfoliated ductal epithelial cells in milk from breastfeeding mothers revealed DNA adducts that resembled 4-aminobiphenyl in structure with P_{32} labeling and had similar peaks as 4-ABP standards in HPLC analysis.[78, 79]

Heterocyclic Amines

Mutagenic heterocyclic aromatic amines (HAAs) are formed when meat is cooked, but also are present in tobacco smoke at lower levels. Identified as risk factors for colon cancer,[80] some HAAs are powerful mammary carcinogens in rodents and may be breast cancer risk factors in humans.[81] In male rats, administration of both 2-amino-1-methyl-6-phenylimidazo[4,5]pyridine (PhIP) and 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) resulted in colon cancer, but females fed IQ and PhIP supplements developed mammary cancer rather than colon cancer.[82]

The human liver activates HAAs such as IQ, 2-amino-3,8-dimethylimidazo [4,5-f]quinolone (MeIQx), and PhIP and, upon activation, hydroxylated metabolites have an increased affinity to covalently bind to the DNA.[83] Although increased consumption of red meat has been linked to increased breast cancer risk,[84, 85] the evidence is inconclusive with respect to a direct association between increased intake of HAAs and breast cancer.[86] A small, hospital-based, case-control study in Uruguay showed an approximately 3-fold increase in risk among women the reporting the highest PhIP intake compared to those reporting the lowest intake.[87] In the NIH-AARP Diet and Health Study Cohort of 120,755 postmenopausal women, after 8 years of follow-up the researchers observed 3,818 cases of breast cancer. This study did not find meat intake or the estimated intake of mutagens/carcinogens to be associated with breast cancer incidence.[88] In a meta-analysis, Kabat and colleagues detected an approximately 17 percent increase in the odds of developing breast cancer when they analyzed 31 epidemiologic studies that had measured meat intake of the participants. This association, however, was not observed when a pooled analysis was performed on eight prospective studies.[88] Furthermore, in the Nurse's Health Study, after 10 years of follow-up and 2,317 breast cancer cases, no association between reported meat consumption and intake of HAAs and increased risk of breast cancer was found.[86] In the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), however, the investigators found a 25 percent increase in risk of invasive breast cancer in women self-reporting the highest intake of red meat. The same magnitude of association (26%) was observed between the highest estimated MeIQx intake and breast cancer.[89] A phase I enzyme of the CYP 450 family, specifically hepatic CYP1A2, is believed to be the main activator of HAAs in hepatic tissue. CYP1A1 and CYP1B1, expressed in the breast, also are capable of activating HAAs to reactive, DNA-adduct-forming metabolites.[83] Although polymorphisms in CYP1A2 that led to higher inducibility and higher carcinogen-activating potential were not linked to an increased risk of breast cancer in a meta-analysis that included 7,580 cases and 10,020 controls,[90] it is plausible that hepatic CYP1A2, as well as CYP1A1 and 1B1 expressed in breast tissue, could interact with HAAs to increase the risk of breast cancer.

N-Nitrosamines

Human exposure to *N*-nitrosamines occurs through diet, endogenous formation in the stomach, tobacco smoke, occupation, and medical therapies.[91] *N*-nitrosamines cause DNA damage[92] such as the promutagenic O^6-methyldeoxyguanosine adducts. Exposure to these compounds also results in decreasing levels of the repair enzyme O6-alkylguanine-DNA alkyl transferase,[93] perhaps increasing susceptibility to nitroso compounds. *N*-nitrosamines also have been shown to cause rodent mammary tumors that are histologically similar to human cancers and can metastasize.[94] In addition, *N*-nitrosamines can transform cultured mouse mammary cells.[92] Cultured human mammary epithelial cells also undergo unscheduled DNA synthesis in presence of these compounds.[76]

Appendix 4. Methodology for Identifying Relevant Funded Breast Cancer Research

National Institutes of Health (NIH)

In 2006, Congress added a requirement in the NIH Reform Act to build a tool to categorize the agency's research. In response, NIH developed the Research, Condition, and Disease Categorization (RCDC) process to categorize funding each fiscal year in 229 research, condition, and disease categories, including breast cancer.

NIH created the Research Portfolio Online Reporting Tools (RePORT) website to provide public access to information on NIH expenditures and the results of NIH-supported research. Included in the tools available on the site is the RePORT Expenditures and Results (RePORTER) System, which allows searching by RCDC categories.

In preparation for the analysis of breast cancer research described in Chapter 7 of this report, data were retrieved from RePORTER in April 2011. Taking into consideration that searching by RCDC category is possible only beginning with fiscal year (FY) 2008 and only for past fiscal years, the Committee included in this report research projects in the RCDC category "breast cancer" that were funded by NIH in from FY2008 to FY2010.

The initial search resulted in 3,004 unique project numbers. As RCDC relies on a text-mining computer application to assign NIH-funded grants and contracts to categories, NIH staff members reviewed each project to ensure its relevance to breast cancer research. Based on this review, 94 projects (0.03%) were excluded from the Common Scientific Outline (CSO) analysis due to their lack of relevance to breast cancer research. The final data set for the CSO categorization included 2,910 active research projects that spanned FY2008 to FY2010.

The CSO code for categories and subcategories provided by the National Cancer Institute (NCI) were used to classify breast cancer grants administered by that Institute. For NCI-related extramural projects, CSO coding is assigned primarily by the NCI Research Analysis and Evaluation Branch (RAEB). For NCI-related intramural grants, CSO coding is assigned primarily by the two NCI intramural divisions—the Division of Cancer Epidemiology and Genetics and the Center for Cancer Research—and coordinated by the NCI Budget Office. If no CSO code was available for a particular project in NCI's internal databases, it was either obtained from the International Cancer Research Partnership (ICRP) website or determined by NIH staff based on the project abstract available in RePORT. Because NCI is the only NIH Institute or Center (IC) that utilizes the CSO to categorize projects, for the purposes of this report, all other NIH grants administered by ICs other than NCI had to be hand-classified by NIH staff using the criteria and examples available on https://www.icrpartnership.org/CSO.cfm. CSO subcategories were retrieved and/or determined only for the Etiology and Prevention categories.

Department of Defense (DoD) Breast Cancer Research Program (BCRP)

Congressional funds allocated to the BCRP are specifically designated by Congress for breast cancer research. Program relevance is one of the programmatic review criteria used to evaluate and select applications for funding. Therefore, all awards funded by the BCRP are directly relevant to breast cancer. Information that includes

abstracts, award amounts, and research categories is publicly available for all BCRP awards using the search engine on the Congressionally Directed Medical Research Programs (CDMRP) website (http://cdmrp.army.mil).

Awards in the BCRP portfolio are assigned codes from both the CSO and a coding system developed by the CDMRP called the Scientific Classification System (SCS). All BCRP applications are assigned two CSO codes and two SCS codes by the Principal Investigators at the time of submission. These initial codes are used to assign applications to peer review panels and to recruit peer reviewers based on the expertise needed. The accuracy of the CSO and SCS codes for funded applications is re-assessed by CDMRP scientists, who review the abstracts and re-assign code(s), if necessary.

Data were retrieved in May 2011. The data shown in Chapter 7, Figure 7.3, on the overall CSO coding of the DoD BCRP portfolio represent FY2006 through FY2010. No exclusion criteria were used.

CSO and SCS codes were used to identify the BCRP's portfolio of environmental research awards funded between FY2006 and FY2010. Awards that included at least one code in the following categories/subcategories were identified as environmental research funded by the BCRP:

- CSO code 2.1: Exogenous Factors
- CSO code: 2.3 Interactions of Genes and/or Genetic Polymorphisms with Exogenous and/or Endogenous Factors
- CSO code 3.1: Interventions to Prevent Cancer: Personal Behaviors that Affect Cancer Risk
- SCS code: Primary Prevention (subcategories: Lifestyle, Chemoprevention, Nutrition)
- SCS code: Biobehavioral Sciences (subcategories: Basic Behavioral, Lifestyle)
- SCS code: Epidemiology (subcategories: Behavioral Epidemiology, Gene and/or Environmental Epidemiology, Nutritional Epidemiology)

Keywords were used to identify any awards that were not captured using the CSO and SCS codes.

Other Federal Agencies

For all other federal agencies (Centers for Disease Control and Prevention, U.S. Environmental Protection Agency, U.S. Food and Drug Administration, and the U.S. Department of Energy) discussed in this report, information was provided to NIH staff by staff members at those agencies.

Nonfederal Organizations

The ICRP database contains project-level funding information from many of the major nongovernmental organizations (NGOs) that fund breast cancer research. NGO data on funded breast cancer research for the years 2005 through 2009 were extracted in May 2012. CSO codes were used to assign projects to the seven major categories. All ICRP funding organizations can submit up to two CSO codes for each funded project, with the percent relevance of each code assigned at 100 percent if only one code is submitted or at 50 percent each if two codes are submitted. Dollar amounts per project and code are allocated by multiplying the total funding by the percent relevance. Data were exported to Excel files for subsequent summarization and graphing. Five-year totals are used in the analysis instead of the annual amounts to improve accuracy.

Appendix 5. Breast Cancer and Environmental Exposures Dissemination and Communication Toolkit

A communication toolkit that incorporates a range of activities, outputs, and impacts is needed to disseminate and communicate information about environmental exposures and breast cancer to a broad range of stakeholders.[95] A number of models and resources from the U.S. Department of Health and Human Services (DHHS), other federal agencies, academic institutions, and international bodies are available to inform the creation of an effective toolkit (see the links at the end of this appendix). This appendix provides the rationale for the creation of a communication toolkit on breast cancer and the environment and the application of federally designed communication models to the development of the toolkit. These models also can be applied to communication about specific research programs.

Rationale for a Communication Toolkit

Communicating information about well-studied environmental agents can prove challenging and underscores the need for strong advance communication plans that are developed in conjunction with proactive research translation and dissemination strategies. Communication about emerging or under-studied issues that raise public concern can require even greater attention to communication strategies.

The table below highlights the potential for communication of research to shape future research, clinical practice, public health activities, individual and community decisions, and policies. The table highlights two examples (1) ionizing radiation, which has relatively strong data linking early exposures to increased breast cancer risk, and (2) endocrine disrupting compounds (EDCs), which represent a newer area of inquiry that has drawn considerable public attention.

For medical imaging, communication needs include educating clinicians and the public to facilitate physician-patient collaboration in decision-making about medical radiation. Communication should include relevant knowledge about appropriate doses of radiation for adults, children, and infants, and the implementation of radiation tracking for patients through electronic medical records.

For EDCs, themes such as the potential action of EDCs at low doses during vulnerable developmental stages and the possible synergy of effects resulting from exposures to multiple EDCs should be communicated. Articulating these themes can provide information needed to inform decisions and protect vulnerable populations.

Examples of Toolkit Activities

- Collect and understand the relevant science.
- Plan the communication: Determine which data to use and develop a storyline.
- Develop the preliminary message, including strategies to address scientific concepts and challenges related to breast cancer and environmental exposures that consider complexity, uncertainty, windows of susceptibility, low-dose exposure to chemicals and radiation, and interactions between environmental exposures, diet, social stressors, and genetics/epigenetics.
- Identify target audiences, including vulnerable populations.

Table A-5.1. Strengthened communication strategies can have wide-reaching effects

Domain	Potential Effects for Enhanced Communication Regarding Ionizing Radiation in Medical Imaging	Potential Effects for Enhanced Communication Regarding EDCs
Future Research	Research is conducted to explore imaging techniques that do not use ionizing radiation. In the absence of these alternatives, research identifies standards for imaging across the life course.	Chemical safety assessment is conducted across the life course for environmentally relevant low-dose exposures. Further, mammary gland development is included as a health end point.
Clinical Practice Guidelines	Clinical guidelines regarding mammography recommendations are harmonized across professional (e.g., American College of Obstetrics and Gynecology), governmental (e.g., HHS), and oversight agencies (e.g., U.S. Preventative Services Task Force).	Clinical guidelines for communicating about and recommending patient health behaviors regarding exposure to EDCs are developed for practitioners who care for pregnant women.
Public Health Recommendations	Public health messages clarify the risks and benefits relevant to breast cancer of various types of medical imaging as well as alternatives for different imaging protocols.	Public health messages communicate concerns about EDCs for breast cancer and provide information on ways to minimize exposure.
Individual and Community Health Choices	Individuals are provided with information to support communication with health care providers regarding screening and diagnostic imaging options. Organizations that support access to care are able to inform their constituencies of risks, benefits, and alternatives so that all communities have access to the best available care.	Individuals and communities are empowered with information and resources to support choices to avoid EDCs.
Policy	Policy addresses the training of technicians who administer imaging tests, the calibration of imaging devices, and coordinated efforts to track patient's exposure to medical radiation.	EDCs are restricted for use in consumer products used during critical periods of development, including by pregnant or nursing women.

- Analyze audience needs and context: Solicit input from stakeholders (including stakeholders from racial/ethnic minority, low-income, and non-native English speaking communities) regarding communication needs related to breast cancer and the environment.
- Plan a dissemination strategy to reach audiences and identify the best communication channels and social networks to reach target communities. Adapt the toolkit to create culturally appropriate modules to reach specific target populations (e.g., African American women, agricultural workers, non-English speakers).
- Conduct formative testing and usability testing with target audiences, including culturally specific modules.
- Disseminate the communication toolkit using social media, blogs, webinars, smart phone apps, and other interactive, web-based tools to reach multiple audiences in culturally appropriate ways (as verified by the analysis of audience needs and context and formative and usability testing).

Examples of Toolkit Outputs

- Draft communication product.
- Final toolkit based on formative and usability testing.

Examples of Toolkit Impact

- Target audiences have a clear sense of the exposures of concern and the personal and societal changes needed to address them.
- Actions are taken to reduce exposure (individual or policy based).
- Advocates have tools and knowledge to educate their constituents about chemicals of concern, other environmentally related risk factors, local and community characteristics, vulnerable subpopulations, and social determinants.
- Improved public health.

Figure A-5.1. Two models of advance planning for health communication related to breast cancer and environmental exposures

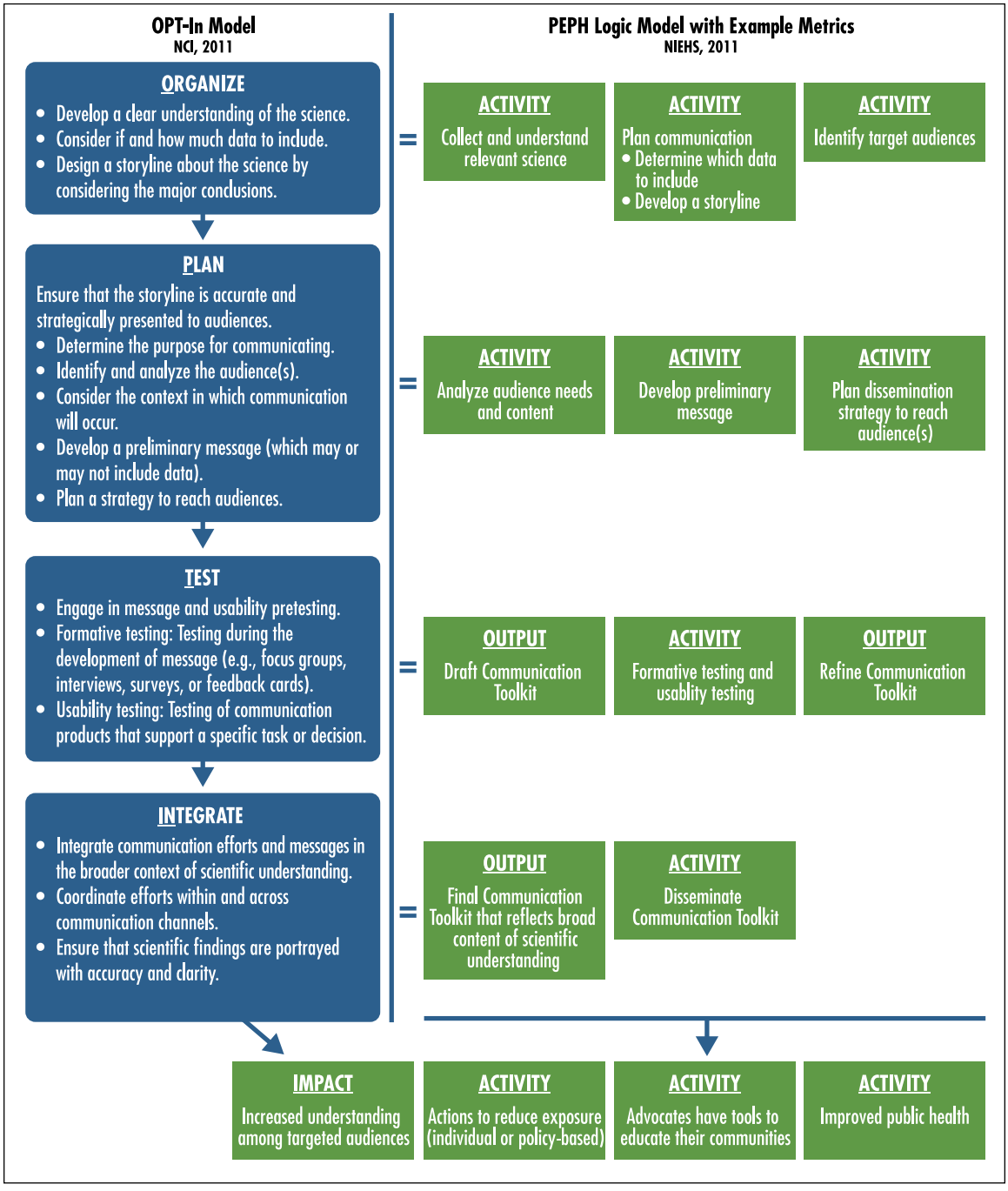

Figure A-5.1 shows two models for developing, testing, and implementing effective communication messages related to breast cancer and the environment. The OPT-In model developed by NCI is shown using the blue boxes on the left. The NIEHS PEPH model is shown using green boxes. The PEPH model assumes that any box can be linked with any other box. Both processes can identify similar activities and outputs, and both can lead to public health activities aimed toward breast cancer prevention.

The toolkit should provide materials that support best practices for the inclusion of stakeholders, training, developing and implementing a communication process, and providing access to knowledge. Some best practices in each of these categories are described below.

Inclusion of Stakeholders

- Develop funding opportunity announcements and requests for proposals that require applicants to include dissemination and communication plans in their study plans. Agencies should provide adequate funding for the development, implementation, and evaluation of research translation and dissemination activities within the grant.
- Plan for research translation and dissemination, which can and should rely on expert communicators to convey the implications of research to all stakeholders, including scientists from the full array of relevant disciplines. In addition, dissemination plans should focus on bidirectional communication rather than simple transmission of information.
- Implement dissemination and communication strategies that engage advocates at the planning and development stages of the research process.
- Provide resources for dissemination and communication of research findings to environmental justice groups that reflect a diversity of race, ethnicity, culture, socioeconomic status, and language of origin.

Training

- Promote breast cancer and environmental health science literacy among advocates, breast cancer survivors, and the concerned public in programs such as Project LEAD[96] and the Environmental Health Trainings at Commonweal.[97]
- Train investigators to appropriately communicate research findings to scientists from other disciplines, decision makers, the media, and the public.

Communication Process

- Encourage the use of dissemination efforts that both push information to intended users and involve pull strategies that engage with the needs and interests of users so that they are drawn to the information.[98]
- Develop materials that are culturally and linguistically appropriate for communicating research findings to diverse communities. Literacy issues should be acknowledged and addressed when developing these materials.
- Use statistics linked with stories to motivate public health policy.[99]
- Communicate research findings so that stakeholders (community members, local agencies, healthcare providers, policymakers, advocates, and community-based experts) understand how each finding affects them and what they can do about it.
- Develop strategies to communicate research to vulnerable and difficult-to-reach populations such as rural, migrant worker, or segregated populations.
- Engage all aspects of the media, including ethnic and linguistically diverse publications, social media, and other contemporary means of communication to increase and sustain awareness.

Access to Knowledge

- Create a comprehensive federal Internet portal through which the public can access information on chemicals, radiation, and other environmental exposures in relation to health. This portal could follow from platforms used in other fields, such as those used for the Morbidity and Mortality Weekly Reports, reports of the agricultural cooperative extension services; or comprehensive web portals similar to those used by the National Library of Medicine's ToxTown (http://toxtown.nlm.nih.gov/flash/city/flash.php) or the National Institute of Environmental Health Sciences (NIEHS) site for the National Toxicology Program (http://ntp.niehs.nih.gov/).

- Support and implement practices that support timely and broad dissemination of research findings, such as publishing accepted peer-reviewed studies online in advance of print, publishing in open-access journals, and employing accelerated peer-review processes.

Resources

- Action Plan to Improve Health Literacy: http://www.health.gov/communication/HLActionPlan/pdf/Health_Literacy_Action_Plan.pdf
- CDC ATSDR A Primer on Health Risk Communication: http://www.atsdr.cdc.gov/risk/riskprimer/index.html
- CDC ATSDR Evaluation Primer on Health Risk Communication Programs: http://www.atsdr.cdc.gov/risk/evalprimer/index.html
- CDC Gateway to Health Communication and Social Marketing Practice: http://www.cdc.gov/healthcommunication/
- CDCynergy: http://www.orau.gov/cdcynergy/web/default.htm
- Communicating Risks and Benefits: An Evidence-based User's Guide: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM268069.pdf
- Communicating Science—A Scientist's Survival Kit: http://ec.europa.eu/research/science-society/pdf/communicating-science_en.pdf
- The Community Toolbox: http://ctb.ku.edu/en/tablecontents/index.aspx
- EPA Risk Assessment and Risk Communication: http://www.epa.gov/agriculture/trisk.html
- Evaluation Primer on Health Risk Communication Programs: http://www.atsdr.cdc.gov/risk/evalprimer/index.html
- FDA Strategic Plan for Risk Communication: http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm183673.htm
- Health Literacy Online: A Guide to Writing and Designing Easy-to-Use Health Web sites: http://www.health.gov/healthliteracyonline/Web_Guide_Health_Lit_Online.pdf
- NCI Risk Communication Bibliography: http://dccps.nci.nih.gov/DECC/riskcommbib/
- NCI Pink Book—Making Health Communication Programs Work: http://www.cancer.gov/cancertopics/cancerlibrary/pinkbook/page1
- NCI Health Communication and Informatics Research: http://cancercontrol.cancer.gov/hcirb/
- NCI Implementation Science: http://cancercontrol.cancer.gov/is/
- Quick Guide to Health Literacy: http://www.health.gov/communication/literacy/quickguide/Quickguide.pdf
- Theory at a Glance: A Guide for Health Promotion: http://www.cancer.gov/cancertopics/cancerlibrary/theory.pdf

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Appendix 6. References

This appendix includes all references cited throughout all of the appendices.

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Glossary

Adjuvant therapy: Additional cancer treatment given after the primary treatment to lower the risk that the cancer will return. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy (http://www.cancer.gov/dictionary?cdrid=45587).

Advocate: An individual who represents and works with an individual or group to promote their rights and interests. Advocates may represent local communities, vulnerable subgroups, and/or a group with special interests (e.g., public health, breast cancer).

Allele: An alternative form of a gene (one member of a pair) that is located at a specific position on a specific chromosome. More than 250 alleles are associated with BRCA1 and BRCA2, which are two genes that can cause a rare, inherited form of breast cancer.

Androgen: A steroid hormone that controls the development and maintenance of masculine characteristics.

Angiogenesis: Development of blood vessels.

Animal-to-human paradigm: An approach that integrates findings from studies of both humans and animals to accelerate scientific knowledge. Animal model studies can be used to generate hypotheses for human studies and aid in interpreting results from human research. Conversely, human studies generate questions that can be tested under controlled conditions with animal models, especially when the time required to conduct the study in humans is too lengthy.

Aromatization: The conversion of androgens into estrogens.

Atypia: An abnormality found in tissue cells.

Bidirectional communication: Communication that moves in two directions. For the purposes of this report, this term refers primarily to communities and advocates providing information and feedback to scientists regarding research activities in addition to scientists providing information to the public.

Carcinogen: A chemical or physical agent capable of causing cancer.

Case-control association studies: Studies that compare people with (cases) and without (controls) a specific disease or condition.

Chemokine: A molecule that helps to regulate the movement of immune cells around the body.

Childhood obesity: A child who is at or above the 95th percentile in body mass index (BMI) for his or her age.

Comparative genomics strategy: An approach that (1) uses an experimental animal model to identify the part of the genome that contributes to risk for a specific disease, such as cancer, and then (2) validates that this part of the genome functions the same way in humans.

Cytokine: A substance that is made by cells of the immune system. Some cytokines boost the immune response; others suppress it.

Differentiation: *In Normal Breast Development*: The process by which a less specialized cell becomes a more specialized cell type. Differentiation changes the cell's size, shape, membrane potential, metabolic activity, and responsiveness to signals. With a few exceptions, differentiation occurs due to highly controlled modifications in gene expression and almost never involves a change in the DNA sequence. Thus, different cells can have different physical characteristics despite having the same genome.
In Cancer: Refers to how mature (developed) the cancer cells are in a tumor. Differentiated tumor cells resemble normal cells and tend to grow and spread at a slower rate than undifferentiated or poorly differentiated tumor cells, which lack the structure and function of normal cells and grow uncontrollably.

DNA double-strand breaks: The severing of both strands of a chromosome's DNA.

Downregulate: A decrease in the number of receptors for a chemical or drug on cell surfaces in a given area in response to an external factor.

Endocrine-disrupting compounds (EDCs): Exogenous chemicals that mimic the function of endocrine systems and may interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormones in the body responsible for the maintenance of homeostasis and regulation of developmental processes (http://www.epa.gov/endocrine/).

Endogenous physiology: Encompasses hormones, growth factors, inflammatory processes, epithelial-stromal interactions, and metabolism originating from within the body.

Environment: Includes all of the surroundings of and influences on living organisms, encompassing a wide range of external influences on breast cancer risk. The complexity of environmental influences on the risk of breast cancer highlights the challenges to research in unraveling this relationship.

Environmental agents: Chemicals or factors in the environment to which humans are exposed that may cause adverse health effects (http://www.niehs.nih.gov/health/topics/agents/index.cfm).

Environmental justice: The fair and equal treatment and meaningful involvement of all people regardless of race, color, national origin, or income with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies.

Eosinophil: A type of white blood cell that contains inflammatory chemicals, highly reactive proteins, destructive enzymes, toxins, muscle contractors, and signaling molecules that can guide immune defenses to the site of infection.

Epigenetic gene silencing: A mechanism of "switching off" a gene through an alteration in genetic structure that does not change the underlying DNA sequence.

Epigenetics: The study of heritable differences in gene expression that occur independent of changes in the primary DNA sequence.

Epithelium: A type of tissue that lines the surface or cavities of the body.

Estrogen receptor: A group of proteins found inside cells that are activated by the hormone estrogen.

Exposure: The condition of being subject to some effect or influence. The effect of any exposure to substances depends on the route of exposure (skin contact, inhalation, ingestion, and injection), duration of exposure (acute or chronic), frequency of exposure, and exposure to other substances.

Expression: The process by which information from a gene is used to create a functional gene product, usually a protein.

Extracellular matrix: Part of the tissue that supports cells.

Extramural research: Research supported by an agency through a grant, contract, or cooperative agreement to non-agency persons and organizations.

Fibroblastic stroma: The connective, functionally supportive framework of the breast tissue.

Fibrocystic breast changes: A common condition marked by benign (noncancerous) changes in breast tissue.

Genetic mutation: A change in the DNA sequence of a gene that may result in the creation of a new character or trait. Genetic mutations can occur spontaneously or can be caused by exposure to ultraviolet or ionizing radiation, chemical mutagens, viruses, and so forth.

Genetic pathway: A group of genes that indirectly interact with each other to contribute to a specific cellular function.

Genetic variant: Differences between individuals' DNA sequences.

Genome-wide analyses: Studies that compare common genetic variations (at many places along their genomes) in persons with and without a disease, health characteristic, or trait.

Genomic: The study of the entire set of genetic instructions found in a cell.

Genotoxicity: The induction of alterations to genetic material. It is a broader term than mutagenicity in that genotoxicity refers to potentially harmful effects on genetic material, which are not necessarily persistent and transmissible. Genotoxicity may be mediated directly or indirectly by chemical or physical agents, and may or may not be associated with mutagenicity.

Global DNA hypomethylation: A genome-wide decrease in the number of methyl chemical groups appended to DNA nucleotides. This epigenetic modification often is associated with cancer.

Grade: The complexity or severity of tumor development at the time of evaluation.

Green space: An area of protected or conserved land or water on which development is indefinitely set aside.

Gynecomastia: Enlargement of the gland tissue of the male breast.

Hazard assessment: The analysis and evaluation of the physical, chemical, and biological properties of a source of potential damage, harm, or adverse health effects.

Health communication: The study and use of communication strategies to inform and influence individual decisions that enhance health. Effective communication is oriented toward the needs of the user, includes various dissemination methods, and draws upon existing resources, relationships, and networks as much as possible.

Health literacy: The capacity to obtain, process, and understand basic information and services to make appropriate health decisions.

Health practice: Clinical practice in medical settings.

Hidden variance: Describes the portion of genetic risk for a common multigenic disease or phenotype that cannot be accounted for by either common Mendelian loci or loci discovered by genome-wide association studies (GWAS). Its origin currently is unknown.

Histone: Proteins that exist in the nucleus of cells, where they interact with DNA by acting as a spool to wrap DNA into compact packets known as nucleosomes, a critical part of the chromatin of the nucleus. Histones control which DNA is transcribed.

Histone deacetylation: Removes acetyl groups from histone tails, causing the histones to wrap more tightly around the DNA and interfere with the transcription of genes by blocking access to transcription factors. The overall result of histone deacetylation is a global (non-specific) reduction in gene expression.

Histone modification: Post-translational modification of histones that occurs by various processes, including acetylation, methylation, phosphorylation, and ubiquitination. These modifications correlate with chromatin structure, gene expression, and function.

Hyperplasia/Hyperplastic growth: An abnormal increase in the number of normal (noncancerous) cells in an organ or tissue.

Implementation science: The study of methods to promote the integration of research findings and evidence into healthcare policy and practice. Implementation science seeks to understand the behavior of healthcare professionals and other stakeholders as a key variable in the sustainable uptake, adoption, and implementation of evidence-based interventions. The intent of implementation science and related research is to investigate and address major bottlenecks (e.g., social, behavioral, economic, management) that impede effective implementation, test new approaches to improve health programming, and determine a causal relationship between the intervention and its impact (http://www.nlm.nih.gov/hsrinfo/implementation_science.html).

In vitro: Taking place in a test tube, culture dish, or elsewhere outside a living organism.

In vivo: Refers to a living organism.

Inbred rodent strains: Mice and rats systematically mated to related parents to create highly genetically similar animals for research.

Intramural research: Research conducted by employees of an agency.

Knock-out mice: Mice genetically engineered to have certain gene(s) inactivated.

Leukocyte: A white blood cell whose chief function is to protect the body against disease-causing pathogens.

Ligand: A molecule that binds to a receptor on the surface of a cell.

Macrophage: A type of white blood cell with two roles: (1) phagocytosis (engulf and then digest) of cellular debris and pathogens; and (2) stimulation of lymphocytes and other immune cells to respond to a pathogen (an agent that causes infection or disease such as a bacterium or virus).

Mast cells: Cells that are part of the immune system. Mast cells reside in different tissues throughout the body, particularly in structures such as blood vessels and nerves, and in proximity to surfaces that interface with the external environment.

Matrix metalloproteinases: Zinc-dependent proteases capable of degrading extracellular matrix proteins that are involved in cell proliferation, migration, differentiation, and apoptosis (cell death); they may influence breast cancer susceptibility.

Meta-analyses: A technique of combining results from different studies to identify patterns and relationships in the findings from multiple studies. A general aim of a meta-analysis is to estimate the true effect size of a finding across multiple studies.

Metastasis: When a tumor spreads from its original location to another part of the body.

Methylation: The addition of a methyl chemical group to the nucleotides of DNA. Hypermethylation refers to an increase and hypomethylation refers to a decrease in this process.

Microenvironment: The breast microenvironment is composed of extracellular matrix (ECM) and numerous stromal cell types, including endothelial and immune cells, fibroblasts, and adipocytes. In breast cancer, the microenvironment consists of cells and molecules surrounding the tumor.

Minority-serving institution (MSI): Post-secondary education institutions classified by the U.S. Department of Education as minority-based on either legislation or the percentage of minority student enrollment.

Molecular signature: A profile of the RNA and DNA expression patterns present within the cells of the breast.

Morphology: The form and structure of organisms.

Mutagen: Anything that causes a mutation (a change in the DNA sequence of a cell). DNA changes caused by mutagens may harm cells and cause certain diseases, such as cancer. Examples of mutagens include radioactive substances, x-rays, ultraviolet radiation, and certain chemicals.

Mutagenicity: The property of being able to induce genetic mutation. These permanent, transmissible changes may involve a single gene or gene segment, a block of genes, parts of chromosomes, or whole chromosomes. Effects on whole chromosomes may be structural and/or numeric (e.g., aberrations and/or aneuploidy). In most cases, mutations involve changes in DNA structure that either have no effect or cause harm.

Neonatal: Shortly after birth (i.e., within the initial 7 days of life). Synonyms: newborn, early postnatal.

p53 null mouse model: A mouse strain that has a nonfunctional p53 tumor suppressor gene.

Paradigm-shifting: Causing a radical change in basic assumptions or approach.

Parity: Number of live births.

Penetrance: The likelihood that a given gene will actually result in disease.

Phagocytosis: The process by which one cell engulfs another cell or particle.

Phenotype: An individual's observable traits, such as eye color or blood type.

Portfolio analysis: An assessment of the elements of an organization's investments to determine the optimal future allocation of its resources.

Precautionary principle: A framework for translating research, such that "when an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically" (1998 Wingspread Statement on the Precautionary Principle). The precautionary principle relies on the weight of the evidence regarding potential hazards, and it increases the scope of relevant science to include research from multiple methods and approaches. It is an analogue to primary prevention in public health.

Prevention, primary: The protection of health by personal and community-wide efforts. Consists of measures aimed at preventing the start of a pathologic process or the occurrence of a disease.

Prevention, secondary: Consists of measures for the early detection of and prompt intervention in a clinically asymptomatic disease (e.g., screening).

Prevention, tertiary: Involves the care of an established disease, with attempts made to restore an individual to his or her highest function, minimize the negative effects of disease, and prevent disease-related complications.

Proliferation: An increase in the number of cells as a result of cell growth and cell division. Abnormally elevated cell proliferation occurs in breast cancer.

Relative risk: A measure of the risk of a certain event happening in one group compared to the risk of the same event happening in another group. A relative risk of greater than one or of less than one usually means that being exposed to a certain substance or factor either increases (relative risk greater than one) or decreases (relative risk less than one) the risk of cancer.

Research diffusion: The process by which new research is communicated among members of a social system. Diffusion often is driven by the needs of an audience.

Research dissemination: Targeted distribution of evidence-based research findings intended to influence health care consumers in ways that ultimately prevent and reduce breast cancer burden in society. Health care consumers may include other health professionals, members of the general public, and program planners and policy makers. Effective dissemination is an interactive exchange between researchers and those with a vested interest in the research.

Research translation: The transfer of scientific discoveries from laboratory, clinical, or population studies into effective interventions at the individual and population level. Research translation involves quantifying and integrating the best new methods and technologies across disciplines and creating tools for high public health impact. Effective translation of research produces usable data as well as information for multiple audiences and multiple uses (e.g., scientific, regulatory, public policy formation, public communication). Collaboration between research producers and research consumers is critical to successful research translation.

Risk: The chance, likelihood, or probability that a person will be harmed or experience an adverse health effect if exposed to a hazard.

Risk assessment: The evaluation of scientific information on the hazardous properties of environmental and other factors, the dose-response relationship (dose-response assessment), and the extent of human exposure to those factors (exposure assessment). The product of the risk assessment is a statement regarding the probability that affected populations or individuals will be harmed and to what degree.

Stakeholder: Refers to a broad range of government agencies, non-profit organizations, communities, professional organizations, researchers, public health and clinical practitioners, media representatives, and individuals invested in environmental exposures and breast cancer.

Transcriptomic: Relates to transcriptome, which is the complete set of messenger RNA molecules (transcripts) produced in a cell or population of cells.

Transdisciplinary research: Research conducted by investigators from different disciplines who collaborate to create new conceptual, theoretical, methodological, and translational innovations that integrate and move beyond discipline-specific approaches to address a common problem.

Transgenic: Refers to an organism that has been engineered to express one or more genes normally found in a different species. Transgenic animals expressing human genes are used routinely to study the functions or pathologies associated with those particular genes.

Tumor suppressor gene: A type of gene that makes a protein that helps to control cell growth.

Tumorigenicity: Capable of producing tumors.

Upregulate: To increase the response to a stimulus; *specifically,* to increase a cellular response to a molecular stimulus due to an increase in the number of receptors on the cell surface.

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Acronyms

AA	aromatic amine
ACBCYW	Advisory Committee on Breast Cancer in Young Women (CDC)
ACS	American Cancer Society
ACToR	Aggregated Computational Toxicology Resource (EPA)
ADH	atypical ductal hyperplasia
AICR	American Institute for Cancer Research
ALH	atypical lobular hyperplasia
AOP	Adverse Outcome Pathway model
ARRA	American Recovery and Reinvestment Act
ATSDR	Agency for Toxic Substances and Disease Registry
AvonFW	Avon Foundation for Women
BCERC	Breast Cancer and the Environment Research Centers (NIEHS and NCI)
BCERP	Breast Cancer and the Environment Research Program (NIEHS and NCI)
BCRP	Breast Cancer Research Program (DoD)
BCSC	Breast Cancer Surveillance Consortium (NCI)
BMI	body mass index
BRFSS	Behavioral Risk Factor Surveillance System (CDC)
BSA	Board of Scientific Advisors (NCI)
CARRA	Consumer Advocates in Research and Related Activities Program (NCI)
CBCRP	California Breast Cancer Research Program
CBE	Communities for a Better Environment
CBPR	community-based participatory research
CCRIS	Chemical Carcinogenesis Research Information System (NCI)
CDC	Centers for Disease Control and Prevention
CEHC	Children's Environmental Health and Disease Prevention Centers (NIEHS and EPA)
CHAMACOS	Center for the Assessment of Mothers and Children
CHSDA	contract health service delivery area
CLAS	Culturally and Linguistically Appropriate Services (HHS)
COEC	Community Outreach and Education Core (University of North Carolina)
COPR	Director's Council of Public Representatives (NIH)
COTC	Community Outreach and Translation Cores (BCERP)
CPCRN	Cancer Prevention and Control Research Network (CDC)
CPDB	Carcinogenic Potency Database (University of California, Berkeley)
CPSC	Consumer Product Safety Commission
CSO	Common Scientific Outline (ICRP)
DCIS	ductal carcinoma *in situ*
DCLG	NCI Director's Consumer Liaison Group

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DCPC	Division of Cancer Prevention and Control (CDC)
DES	diethylstilbestrol
DoD	U.S. Department of Defense
ECR	Early Career Reviewer Program (NIH)
EDC	endocrine-disrupting compound
EGF	epidermal growth factor
EPA	U.S. Environmental Protection Agency
ER	estrogen receptor
ERC	European Research Council
FDA	U.S. Food and Drug Administration
FSH	follicle stimulating hormone
GAO	U.S. Government Accountability Office
GH	growth hormone
GWAS	genome-wide association studies
HAN	hyperplastic alveolar nodule
HER2	human epidermal growth factor receptor 2
HGF	hepatocyte growth factor
HHMI	Howard Hughes Medical Institute
HHS	U.S. Department of Health and Human Services
HT	hormonal therapy
HTRA	high-throughput risk assessment (EPA)
IARC	International Agency for Research on Cancer
IBC	inflammatory breast cancer
IBCERCC	Interagency Breast Cancer and Environmental Research Coordinating Committee
IC	Institutes and Centers (NIH)
ICRP	International Cancer Research Partnership
IGF-1	insulin-like growth factor-1
IOM	Institute of Medicine
LAN	light at night
LH	luteinizing hormone
LIBSCP	Long Island Breast Cancer Study Project (NCI and NIEHS)
MEC	Multiethnic Cohort Study (NCI)
MRI	magnetic resonance imaging
NAACCR	North American Association of Central Cancer Registries
NBCC	National Breast Cancer Coalition
NBCCEDP	National Breast and Cervical Cancer Early Detection Program (CDC)
NCATS	National Center for Advancing Translational Sciences (NIH)
NCCAM	National Center for Complementary and Alternative Medicine (NIH)

NCCT	National Center for Computational Toxicology (EPA)
NCEH	National Center for Environmental Health (CDC)
NCGC	NIH Chemical Genomics Center
NCI	National Cancer Institute (NIH)
NCPHCELC	National Conversation on Public Health and Chemical Exposures Leadership Council
NCRR	National Center for Research Resources (NIH)
NCTR	National Center for Toxicological Research (FDA)
NFO	nonfederal organization
NGO	nongovernmental organization
NHANES	National Health and Nutrition Examination Survey (CDC)
NHGRI	National Human Genome Research Institute (NIH)
NHIS	National Health Interview Survey (CDC)
NHLBI	National Heart, Lung, and Blood Institute (NIH)
NIA	National Institute on Aging (NIH)
NIBIB	National Institute of Biomedical Imaging and Bioengineering (NIH)
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development (NIH)
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases (NIH)
NIEHS	National Institute of Environmental Health Sciences (NIH)
NIGMS	National Institute of General Medical Sciences (NIH)
NIH	National Institutes of Health
NIMHD	National Institute on Minority Health and Health Disparities (NIH)
NIOSH	National Institute for Occupational Safety and Health (CDC)
NPCR	National Program of Cancer Registries (CDC)
NRC	National Research Council
NRSA	Ruth L. Kirschstein National Research Service Award (NIH)
NTP	National Toxicology Program (NIH, CDC, FDA)
OBSSR	Office of Behavioral and Social Sciences Research (NIH)
OCSPP	Office of Chemical Safety and Pollution Prevention (EPA)
OHAT	Office of Health Assessment and Translation (NTP)
ONES	Outstanding New Environmental Scientist award (NIEHS)
ONSF	Oncology Nursing Society Foundation
OSHA	Occupational Safety and Health Administration
OWH	Office of Women's Health (FDA)
PEHSU	Pediatric Environmental Health Specialty Unit (ATSDR, EPA)
PEPH	Partnerships for Environmental Public Health
PIP	Public Interest Partners (NIEHS)
P.L.A.N.E.T.	Plan, Link, Act Network with Evidence-based Tools (NCI)
PR	progesterone receptor

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Project LEAD	Leadership, Education, and Advocacy Development (NBCC)
PROSPR	Population-Based Research Optimizing Screening through Personalized Regimens (NCI)
PUFA	polyunsaturated fatty acid
QTL	quantitative trait loci
RCMI	Research Centers in Minority Institutions Program (NIMHD)
REACH	Registration, Education, Authorization, and Restriction of Chemicals (European Union Act)
RePORT	Research Portfolio Online Reporting Tools (NIH)
ROC	Report on Carcinogens (NTP)
RTIP	Research-Tested Intervention Program (NCI)
SEER	Surveillance, Epidemiology, and End Results Program (NCI)
SES	socioeconomic status
SLN	sentinel lymph node
SNAP	Supplemental Nutrition Assistance Program (USDA)
SPARCCS	Survey of Physician Attitudes Regarding the Care of Cancer Survivors (NCI)
STAR	Study of Tamoxifen and Raloxifene (NCI)
TDLU	terminal ductal lobular unit
TEB	terminal end bud
TGF	transforming growth factor
TNBC	triple-negative breast cancer
TSCA	Toxic Substances Control Act
WHI	Women's Health Initiative (NHLBI)
WHO	World Health Organization
USDA	U.S. Department of Agriculture
VA	U.S. Department of Veterans Affairs
VOC	volatile organic compound
WIC	Women, Infants and Children (USDA)