Introduction

Researchers have long accepted that breast cancer is a complex disease and that both genetic and environmental factors individually contribute and interact with each other to increase breast cancer risk. The identification of different environmental factors that influence breast cancer risk presents a tremendous opportunity to prevent breast cancer. Yet to date, relatively little of the breast cancer research funded by the NIH has focused on environmental health. An exception to this is the Breast Cancer & the Environment Research Program (BCERP), a joint effort by the NIEHS and the NCI, which began in 2003 and was renewed in 2010. The BCERP represents one of the first initiatives to directly examine the influence of exposure to environmental chemicals at likely windows of susceptibility, such as puberty, to evaluate how environmental exposure influences early events that may affect the risk for female breast cancer. This is important since lack of progress in identifying environmental determinants of breast cancer risk may be attributable in part to the focus of previous research on adult exposures after the relevant windows may have passed. In addition, the BCERP is a unique transdisciplinary program that strives to combine epidemiologic, basic and social science, and the participation of advocate communities to better understand and advance breast cancer prevention. This approach is vital to stimulate new research approaches and accelerate translation of research findings into disease prevention.

A major goal of the BCERP is to ensure that new findings are appropriately translated and disseminated to girls and women at risk through engagement of breast cancer advocates and other community groups. Towards this goal, BCERP has supported a wealth of community engagement forums and produced numerous outreach materials, including the BCERP toolkits (described in more detail below). It also has held annual public meetings that engage researchers, trainees, and advocates and provide an opportunity to disseminate findings from the program and to raise the environmental health literacy of participants.

The BCERP has provided a transdisciplinary framework for enhancing research and translation among collaborators of varied expertise. A number of scientific advances have emerged from the BCERP. Examples of recent key scientific findings include:

- Puberty, as indicated by onset of breast development, is occurring in white girls at even younger ages than reported in previous publications. However, black girls continue to experience breast development earlier than white girls. Earlier onset of puberty in girls is also strongly associated with greater body mass index (BMI)(1).

- Peripubertal urine concentrations of high-molecular-weight phthalate metabolites were inversely associated with pubic hair development at one year follow-up in BCERP girls. A weak positive trend (earlier development) was observed for low-molecular-weight phthalate biomarkers with breast and pubic hair development (2).

- Perfluorooctanoate (PFOA) was found at high concentrations in the blood of peripubertal girls who were breast fed. Subsequent BCERP experimental studies in mice found peripubertal PFOA exposure was associated with a delay in pubertal outcomes and reduced...
expression of mammary growth factors. Data were translated to policy and used to inform water district officials (3)(4).

- Research in women with breast cancer found two biologically-defined extratumoral gene expression signature subtypes: Active subtype, which is associated with high expression of genes related to fibrosis and wound response, and an Inactive subtype, which has high expression of cellular adhesion genes. Subtypes are strongly associated with mammographic density and breast tissue composition (5).

- Pubertal exposure of rats to high fat diet can increase carcinogen-induced mammary cancer risk in adulthood and reduce tumor latency with or without an effect of weight gain and risk is not reversed by switching to a low fat diet in adulthood (6).

- Prenatal exposure of rats to bisphenol A (BPA) increases mammary cancer susceptibility in the offspring and shifts the time of susceptibility for chemically-induced mammary carcinogenesis. BPA exposure of nursing offspring and chronic exposure to BPA in adulthood also have been shown to influence mammary gland carcinogenesis, suggesting multiple potential windows of susceptibility (7-9).

- Prenatal exposure of rats to butyl benzyl phthalate (BBP) results in delayed pubertal onset, altered mammary morphology and gene expression at puberty and also shifts the proliferative index in almost all mammary epithelial structure. However, BBP does not appear to increase the risk or characteristics of chemically-induced tumors in rats (10, 11).

- Researchers identified GATA3 as the master regulator gene in mammary gland development and demonstrated it promotes differentiation, suppresses metastasis and alters the tumor microenvironment by inducing miR-29b expression. This discovery suggests that the GATA3-miR29b axis may be a target for therapeutic intervention in breast cancer (12, 13).

- Focus groups of mothers with young daughters evaluated the effectiveness of translating and disseminating information about environmental breast cancer risks using a magazine-style format. Results indicated mothers desire greater scientific detail but presented in a more reader friendly format that includes greater explanation of findings (14).

Concurrently, under the 2008 Breast Cancer and Environmental Research Act, the NIEHS and NCI led the Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC). The goals of the IBCERCC were to develop a report to outline the current state of breast cancer and the environment research; identify key research questions, methodologies, and knowledge gaps that must be addressed to move this field forward; and make recommendations for accelerating the identification and mitigation of the environmental causes of breast cancer.

In the next phase of the BCERP program, the NIH BCERP staff aims to build upon emerging findings from the BCERP while also drawing upon the expert recommendations of the IBCERCC. The program will stress an overall focus on transdisciplinary research that takes a life-stage approach to the study of breast cancer (including consideration of breast cancer subtypes) and the environment. We also propose a new communications research component to evaluate and adapt existing messages about the role of environmental exposures in breast cancer risk.

**Research Goals and Scope**

The overarching goal of the Breast Cancer & the Environment Research Program (BCERP) is to support integrated scientific research to enhance our knowledge of environmental and genetic
factors underlying breast cancer risk in study populations across diversity of ethnic/racial groups and throughout the lifespan. The next phase of the program will build upon current successes of the BCERP by:

- **Expanding investigation to other intermediate risk factors for breast cancer.** To date, human studies supported under BCERP have predominately focused on timing of pubertal development (e.g., age at onset of breast development, age at menarche) as an intermediate risk factor for breast cancer. The next phase of the program will encourage investigation of additional intermediate risk factors for breast cancer, such as high breast density and benign breast disease. The goal is to expand our understanding of predictive markers of changes in the mammary gland at specific life stages, to understand how they are impacted by environmental exposures and provide opportunities for complementary mechanistic studies.

- **Expanding investigations of windows of susceptibility.** To date, exposures time points examined by the BCERP have largely focused on early exposure windows. A goal moving forward is to expand investigations to other windows, such as post-puberty adolescence, time at first birth and menopause, and achieve greater balance across scientific disciplines and populations studied (e.g., expand our knowledge of how environmental exposures impact women of color). There is also a need to further explore additional exposures and mechanisms within windows already under investigation.

- **Providing opportunity to confirm findings of animal studies in human studies and vice versa.** Numerous scientific findings have been generated from the basic science and epidemiological components of BCERP as well as other investigators in the field. A goal moving forward is to place even greater emphasis on leveraging existing knowledge, community partner interests and the creation of transdisciplinary teams in generating research hypothesis and study designs.

- **Promote greater coordination with the broader research communities.** BCERP has utilized a number of tools, such as annual integration and public scientific meetings and an Opportunity Fund, to stimulate cross-project collaboration within the BCERP. A goal moving forward will be to expand the reach of the program by attracting other needed expertise and investigators in this field and closely related ones. A related goal will be to reach out to other federal partners with an interest in breast cancer and the environment by including them in BCERP working groups.

- **Validate and Implement Environmental Health Communications Related to Breast Cancer.** Community partners engaged in the BCERP program have expressed a need for evidence-based tools and communication strategies about environmental risks for breast cancer. The existing BCERP communication toolkits are one of many efforts to disseminate information to increase knowledge and awareness about environmental risk factors for breast cancer, and to spur preventive action, where applicable. A goal for the next phase of BCERP is to adapt, validate, and disseminate risk communication messages from the BCERP toolkits and other existing communication materials, and to assess resultant individual-level behavior change and policy-level public health strategies to reduce risk.

**Overall Concept Structure**

The next phase of the BCERP will take a multi-pronged approach, in which two coordinated research initiatives are released. The first initiative, henceforth referred to as the BCERP
Transdisciplinary Research Initiative, will entail release of two companion Funding Opportunity Announcements (FOAs), one to support a group of individual research projects with community-academic partnerships, and one to support a Coordinating Center to integrate efforts across the network of individual projects. The second initiative, henceforth referred to as the BCERP Communication Research Initiative, will entail a set of companion Funding Opportunity Announcements (FOAs) to support small communication research grants to assess and/or translate environmental health messages related to breast cancer risks using the R03 and R21 mechanisms. Details of the two initiatives are provided below.

**BCERP Transdisciplinary Research Initiative**

As described above, the BCERP Transdisciplinary Research Initiative will be comprised of a consortium of individual research projects and a Coordinating Center. For purposes of this initiative, transdisciplinary research is defined as research that involves scientists from multiple disciplines, spanning human and animal/in vitro-based research, as well as community partners working interactively on a common problem to develop novel cross-disciplinary methods, insights, and research approaches that would not have occurred with a traditional uni-disciplinary investigation. All BCERP projects will work collaboratively with the BCERP Coordination Center and NIH staff to establish shared resources that support needs across the initiative and maximize the collaborative nature and impact of the program.

**Key Questions the BCERP Transdisciplinary Research Initiative can Collectively Address**

- Which classes of environmental exposures influence and/or interact with intermediate risk factors to increase breast cancer risk?
- What are the underlying mechanisms linking environmental exposure at different life stages, alterations in the mammary gland, risk factors and breast cancer?
- How do genetics, social determinants of health, and lifestyle factors modify the impacts of environmental exposures and jointly contribute to the overall risk of breast cancer?
- What strategies for prevention are indicated by the connections between exposure, observable factors, and underlying mechanisms?
- How can findings be best translated into effective risk messages for various communities or to inform policy?

**Scope of Individual Research Projects**

Individual BCERP project applicants will be required to submit proposals for studies that work across the in vitro/animal-to-human research paradigm and propose new transdisciplinary hypotheses that can be tested in a complementary manner in both human studies and experimental exposure studies using in vivo in vitro models. Individual BCERP research projects will be focused on a central theme and include 2 to 3 transdisciplinary research aims as well as appropriate aims to engage community partners.

Elements of individual projects will include:

- *Community-academic partnerships*. The inclusion of advocates and community organization representatives in research planning and prioritization allows for the integration of their unique perspectives and expertise into identifying research priorities. Community partnerships also facilitate bi-directional communication between researchers and the
engaged community at the individual project level and help ensure that research findings are appropriately translated and disseminated to diverse public audiences and that. The BCERP community partners as a group will continue to play a central role in integrating, translating, and disseminating findings from across the Program to inform national, state and local policy and public health initiatives.

- **Address a specific window(s) of susceptibility.** 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. Epidemiologic and experimental animal evidence is accumulating that demonstrates differences in mammary cancer risk associated with environmental exposures at different stages—referred to as “windows of susceptibility.” The goal of BCERP is to clearly address relevant windows of susceptibility in study design that will lead to improved insights into which exposures and genetic predispositions likely lead to altered risk and the mechanisms by which earlier exposures lead to breast cancer to develop preventive strategies.

- **Transdisciplinary research approach.** The integration of laboratory (i.e., animal and *in vitro*) and human research offers an opportunity to understand the contribution of environmental factors to breast cancer risk, the underlying mechanisms, and the potential for prevention strategies. Integration of findings from both areas of expertise accelerates scientific knowledge and may improve the understanding of the applicability of animal/*in vitro* models to human research. Furthermore, the inclusion of breast cancer advocates and other community representatives in research projects helps accelerate translation of research findings into risk communications and breast cancer prevention.

- **Focus on intermediate risks factors that precede breast cancer.** For purposes of this initiative, an intermediate risk factor is defined as an established risk factor for breast cancer that may be attributable to a shared etiological pathway(s) linking environmental exposure(s) at specific life stages with future disease. These factors should be observable in humans prior to breast cancer occurrence and may serve as predictive markers of environmentally induced breast cancer risk. Despite advances in our understanding of how environmental exposures influence some aspects of pubertal development, in particular breast development, many questions remain regarding the influence of environmental exposures on other intermediate risks factors. Such factors include additional markers of pubertal development and growth, breast density and benign breast disease. The role of environmental exposures in influencing breast density and benign breast disease is largely unknown and of increasing interest to the scientific and breast cancer advocacy communities. Studies should be designed to accelerate understanding of the influence of the environment on such intermediate factors.

**Scope of the Coordinating Center**

The Coordinating Center will provide intellectual and scientific leadership as well as logistical support to the overall network. A primary role of the Coordinating Center will be to identify commonalities in research questions being explored across sites and opportunities to extend the transdisciplinary nature of the program. The Coordinating Center will:

- Identify research activities across projects that could be integrated or standardized to minimize duplication and maximize utilization of existing resources.
- Identify scientific problems that could be jointly explored and coordinate development of
collaborative projects.

- Oversee an “Opportunity Fund” pilot project program to help support new transdisciplinary research questions that emerge from the program.
- Establish and coordinate topical “Expert Working Groups” around key scientific issues that cross-cut individual projects, and help identify other investigators working in relevant research fields but not directly funded by BCERP to join these working groups (such as other NIH intramural and extramural investigators and other federal partners).
- Provide logistical and administrative support for network activities by providing state of the art cross-project communication, a project web site, and working with program staff and Principal Investigators (PIs) to organize the biannual meetings.
- Assist NIH Staff in regularly reviewing the program to assess whether transdisciplinary goals are being met.
- Serve as research data management center (as appropriate).

Because of the strong intellectual leadership role the Coordinating Center will play, it is anticipated that Coordinating Center personnel will have expertise and strong prior experience in e.g. biostatistics, evaluation and team science, and a record of excellence in coordinating large multi-site programs, providing logistic infrastructure, and organizing related dissemination programs.

**Scope of the BCERP Communications Research Initiative**

Communications about research findings have become increasingly important as scientific and health literacy grows among the general public, and advocates and activists express the need to understand and disseminate the significance of research that is relevant to themselves, their families and communities. The BCERP program was initially developed to leverage the interest and engagement of these individuals and organizations, and they have been actively engaged and committed to the successful implementation of the research as well as the appropriate dissemination of findings.

From 2011-2013, BCERP program staff developed key message toolkits based on the research findings. These toolkits were developed as targeted health risk messages for specific audiences, including toolkits for general parents/caregivers, for African-American parents/caregivers, for health professionals, and for breast cancer organizations to use in their outreach and dissemination efforts. In addition, BCERP Community Outreach and Translational Cores and Community Partners (COTCs/CPs) have been engaged in translation of BCERP findings into effective messages for their local communities in culturally appropriate formats and languages. The COTC/CPs have utilized the toolkits in their outreach efforts and, in some cases, further adapted the materials for various age groups and literacy levels.

Concurrently, the IBERCC report outlined recommendations that included the development of culturally appropriate, evidence-based messaging. In response to these recommendations, and the community-expressed need to further adapt existing educational materials for additional audiences, NIH staff is proposing targeted funding to explore the efficacy of health risk messaging on environmental exposure risks for breast cancer. The BCERP Communication Research Initiative will support research in the following areas:
• Evaluation of the level of cultural acceptance of breast cancer and the environment risk messages in different ethnic and socioeconomic settings, which would assist in crafting effective messages
• Assessment of the effectiveness and understandability of existing educational materials to inform individuals of heightened risks or about the utilization and sustainability of existing evidence-based tools and approaches
• Confirmation of the ability of messaging about environmental factors to actually impact behavior change or lead to the reduction of the environmental exposures of concern

Ultimately, the research outcomes of this initiative will help identify and promote communication practices and resources that effectively translate the findings of research into individual behavioral change, public health strategies, clinical practice, and community initiatives to reduce exposures and breast cancer risk.

**Mechanism and Justification**

**Mechanisms:**
The BCERP Transdisciplinary Research Initiative will use a cooperative agreement (U01) mechanism for both individual projects and the Coordinating Center. Two companion FOAs will be released simultaneously to solicit applications for these two components of the initiative.

The BCERP Communications Research Initiative will use both the R21 and R03 mechanism. Two companion FOAs will be released simultaneously for the two different grant mechanisms.

**Timeline:**
The BCERP Transdisciplinary Research Initiative will be released in summer 2014. The BCERP Communications Research Initiative will be released 3-6 months later.

**Budget and Initiative Periods**
The total cost of FOAs for both the transdisciplinary research and communication research initiatives will be $38.0M over five years and will be shared between NIEHS (60%) and NCI (40%). The breakdown of cost by initiative and cost by NIH Institute are shown below in table 1. It is anticipated that funding for the transdisciplinary research initiative will span fiscal year (FY) 2015-2019 and the communication research initiative will span FY2016-2017.

<table>
<thead>
<tr>
<th>Initiative</th>
<th>Length of Program</th>
<th>Total cost/year</th>
<th>Cost/Year for NIEHS</th>
<th>Cost/Year for NCI</th>
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<tr>
<td>Transdisciplinary Research (FY15-19)</td>
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<td>$7.2 million</td>
<td>$4.2 million</td>
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<tr>
<td>Communication Research (FY16-17)</td>
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<tr>
<td>Years with Concurrent Initiative Funding (FY16-17)</td>
<td>2</td>
<td>$8.2 million</td>
<td>$4.8 million</td>
<td>$3.4 million</td>
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**Justification for the RFA:**
• As was recommended in the IBCERCC report, the time is ripe for translation of research findings across both population- and laboratory-based studies. For example, the potential
relevance of an observed delay in breast development in girls with higher phthalate exposure for future breast cancer risk is optimally answered in animal/laboratory-based studies. Conversely, novel biomarkers of early onset of pubertal development that have been identified in animal models and could ostensibly be predictors of eventual breast cancer must be tested for relevance in human populations.

• BCERP took a first, critical step towards understanding the nature and mechanisms of early environmental exposure on established risk factors for breast cancer. It is among a few pioneering programs addressing the Windows of Susceptibility concept in breast cancer; and fewer still that directly measure exposure, longitudinally follow subjects, and intersect with laboratory studies to explore cellular and molecular mechanisms of changes in risk factors. Follow up is needed to build on the initial studies and continue to identify early exposures, the limits of Windows of Susceptibility, and molecular pathways that are sensitive to environmental influence. The optimal construction of public health messages and strategies around environmental causes of breast cancer also remain unclear.

• New technologies have come on board. For example, technologies to allow enrichment of mammary gland stem cells, 3D culture models which better reflect the tissue environment found in vivo, imaging technologies that allow the exploration of the dynamic interactions that occur during mammary gland development and neoplasia both in vitro and in vivo, and significant progress in generating humanized mouse models that allow new experiments, such as implanting and growing primary human cancer cells in the cleared mammary fat pad of immunocompromised mice.

• The incidence and frequency of breast cancer remain areas of great public health and community concern, with associated strong scientific interest.

Justification for Use of a Cooperative Agreement
The BCERP will be jointly supported and managed by NIEHS and NCI. The Program will support a network of cooperative agreements (U01) comprised of individual research projects and a Coordinating Center that will work across the program on transdisciplinary and communication research projects. A cooperative agreement program is necessary to ensure coordination, to accelerate progress toward understanding mechanisms linking environmental exposures and breast cancer, and to translate and disseminate findings to the public. It is expected that all of the awarded BCERP projects will work together to minimize duplication, and as appropriate, utilize common resources, assessment tools and methodologies. Furthermore, these complex projects will require NIEHS and NCI staff oversight and involvement at multiple levels. NIH program staff will:

• Participate on the BCERP Steering Committee and various working groups to be established by the BCERP Coordinating Center.

• Participate in the planning and oversight of all activities organized by the Coordinating Center, such as dispersion of pilot project funds, organization of meetings, production and evaluation of messages, national scientific sessions, and message dissemination.

• Interact with the project investigators and outreach experts on constructing and disseminating public health messages on the impact of environmental stressors on the development of the mammary gland.

• Monitor and assess the performance of the BCERP in achieving its goals as outlined above.
Bibliography