

The Breast Cancer and the Environment Research Centers

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The Breast Cancer and the Environment Research Centers (BCERCs) were among the last large-scale scientific undertakings championed by Dr. Kenneth Olden at the National Institute of Environmental Health Sciences (NIEHS). These centers were the culmination of years of discussion and planning within the National Institutes of Health (NIH) and with both the scientific and advocacy communities. They stand as a tribute to Dr. Olden's unique perspective on the value of interdisciplinary science and the participation of communities and concerned citizens in publicly funded science projects.

A Major Public Health Problem

The BCERCs address a major public health problem with an innovative scientific approach. Breast cancer remains the most common invasive cancer among women in this country, with an estimated 211,240 new cases and 40,410 deaths to occur in 2005 (Jemal et al. 2005). After neoplasms of the lung, breast cancer is the second leading cause of cancer deaths for women. The burden of this disease, however, goes beyond the statistics because it strikes many women in mid-life during their most productive years, and the psychosocial impact of this cancer on its victims and their families is life altering. Environmental causes have long been suspected because of the substantial international variation in incidence and mortality rates and the surprisingly rapid increase in rates that can follow the immigration of populations with low rates of breast cancer into societies with high rates (Stewart and Kleihues 2003). Genetic susceptibility, on the other hand, probably accounts for no more than 10% of new cases. It has been accepted for some time that the environment, not genetics, is the most powerful force in breast carcinogenesis.

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The search for just what it is about the “environment” in industrialized countries that increases the risk of breast cancer has been long-standing and intense. Scientists have examined and are continuing to study multiple potential explanations, including the changing reproductive patterns of modern women, dietary factors (especially dietary fats), reduced physical activity patterns, medicinal drug use, and toxic aspects of the physical environment (Stewart and Kleihues 2003). Consequently, much is understood about the etiology of breast cancer. Family history and reproductive factors such as early age at menarche, late age at menopause, and late age at first birth have long been established risk factors; use of hormone replacement and alcohol both confer minor increased risk (Henderson et al. 1996). But much about the causes of breast cancer remains unclear. The role of potential carcinogens in the physical environment has consistently been a public concern (Gammon et al. 2002; Marin County Town Meeting 2002), and there is still much to learn about the measurement of exposures to environmental toxins and their possible role in the etiology of breast cancer.

The BCERCs were created as a result of continuing public concern and lack of scientific evidence to convincingly rule in or out the role of environmental chemicals in breast cancer etiology. Dr. Olden was key to the process that led to the formation of these centers.

Preceding Events

A number of notable events led to the formation of the BCERCs. These included multiple conferences and research projects that tried to address concerns about environmental etiologic factors in areas with a high incidence of breast cancer (Clarke et al. 2002; Gammon

et al. 2002). In April 2002 an NIEHS brainstorming session on breast cancer and the environment was held in Charlotte, North Carolina. The meeting was co-chaired by Dr. Olden and Frances Visco, president of the National Breast Cancer Coalition (NBCC), to explore the opportunity to create Centers of Excellence for the study of breast cancer. Dr. Olden invited not only respected scientific experts but also consumers and public interest groups to provide a full range of commentary and perspectives on breast cancer causes and prevention. Major topics of discussion included genetics and toxicogenomics in the developing mammary gland, windows of susceptibility to breast carcinogenesis, molecular epidemiology, animal models, and the role of consumers, community, and breast cancer advocates. The difficulty in obtaining funding for the type of long-term interdisciplinary research needed for innovative breast cancer research was a concern expressed by attendees.

Later, in May 2002, the International Summit on Breast Cancer and the Environment: Research Needs, a major international conference, was convened on 22–25 May 2002 in Santa Cruz, California, under the auspices of the Centers for Disease Control and Prevention, the International Agency for Research on Cancer, and the NIEHS Center on Environmental Health Sciences at University of California Berkeley. The conference focused the attention of numerous experts from the full disciplinary spectrum on the continuing need for study of environmental factors in breast cancer with substantial input from the advocacy community. At that conference Dr. Gwen Collman from the NIEHS reported on the plans for breast cancer centers that would fill existing gaps in knowledge with interdisciplinary research while recognizing the importance of community participation.

During this time advocacy groups led by the NBCC lobbied Congress to support additional NIH funding for centers of excellence in breast cancer and the environment. Although no additional funds were designated by Congress, Dr. Olden took it upon himself and the NIEHS to redirect funds previously allocated to other projects and to work with the National Cancer Institute (NCI) to identify additional monies that could be devoted to this purpose.

Dr. Olden visited Marin County, California, in October 2002 at the invitation of Marin Breast Cancer Watch, a local advocacy group, for one of the town meetings for which he was so well known. He engaged with the community and local breast cancer advocates on their concerns and how federal research and public health agencies could respond to them. This town meeting, like many of those held by Dr. Olden during his tenure as director of NIEHS, brought his genuine concerns for environmental health and his warmth as a human being directly to the communities most affected by environmental concerns. He chose this occasion to announce the imminent release of the Request for Applications (RFA) for Breast Cancer and the Environment Research Centers (NIEHS/NCI 2002).

In November 2002 the RFA was released in partnership with the NCI, calling for a network of research centers comprising interdisciplinary scientific teams to focus on “how chemical, physical, biological, and social factors in the environment work together with genetic factors to cause breast cancer” (NIEHS/NCI 2002). Two types of projects were called for: one using animal models to characterize pathways related to breast and endocrine system development over the life course, and a second to conduct an epidemiologic study of the determinants of puberty in girls. As an overall goal the centers were

to integrate the basic biological, toxicologic, and epidemiologic data on the development and life span of the mammary gland in a way that public health messages can be designed to educate young girls and women who are at high risk of breast cancer on the role of specific environmental stressors in breast cancer development. (NIEHS/NCI 2002)

One of the novel aspects of the RFA, which Dr. Olden strongly supported, was the requirement that each center would have a Community Outreach and Translation Core (COTC), thus ensuring that support would be provided to facilitate continuing input from and feedback to the communities that had spoken so clearly about

the need for new breast cancer and environmental research in the first place.

In late 2003 the creation of four BCERCs was announced, with funding of \$35 million over 7 years, an unusually long duration for such awards (Claudio 2004). These were cooperative agreements that provided for ongoing collaboration between the NIH sponsors and center scientists. Partial support came from the NCI.

Clearly the input of the scientific and advocacy communities was heard by Dr. Olden and his colleagues at the NIEHS. To emphasize his support, he personally attended a kickoff event in Marin County on 14 October 2003, that included many of the local breast cancer advocates, public officials, principal investigators from all four centers, and scientists from the new University of California San Francisco (UCSF) bay area center.

The Breast Cancer and the Environment Research Centers

The four BCERCs are led by the Fox Chase Comprehensive Cancer Center in Philadelphia, Pennsylvania; Michigan State University in East Lansing, Michigan; the University of Cincinnati in Cincinnati, Ohio; and the University of California San Francisco Comprehensive Cancer Center in San Francisco, California, although many of the centers are consortia of several institutions.

FOX CHASE COMPREHENSIVE CANCER CENTER

Directed by Dr. Jose Russo, this center also includes in its leadership Dr. Coral Lamartiniere at the University of Alabama Comprehensive Cancer Center in Birmingham, Alabama, and Dr. Mary Wolff of the Mt. Sinai School of Medicine in New York City, who directs the epidemiologic study conducted in Manhattan, which is focused on Latina and African-American girls. This center is using the rat model to determine the effects of prepubertal endocrine disruptors on proteomic and genomic signatures of the mammary gland during critical stages of development and differentiation. Xenobiotics of interest include bisphenol A, butyl benzyl phthalate, and tetrachlorodibenzo-*p*-dioxin (TCDD). Animals are being dosed and proteomic analysis protocols are being developed in the laboratory of Dr. Lamartiniere, and rat mammary glands are being prepared for genomic studies in Dr. Russo's laboratory. These protocols are shared

with the other three centers in the BCERC network to aid in standardizing procedures among centers and in keeping with the spirit of collaborative research intended by the NIH.

In the epidemiologic project being carried out in East Harlem, Dr. Wolff and her colleagues are recruiting 600 girls 7–8 years of age, who are about 40% African American and 60% Latina, from wellness visits at pediatric or school-affiliated clinics. Annual physical examinations and interviews are planned for collection of information on the determinants of pubertal maturation and the study of outcomes that include the ages when girls reach critical stages of pubertal development (i.e., Tanner stages), menarche, and the duration of time between Tanner stage B2 and menarche (i.e., tempo). Special interests of the investigators at this center include measurement of single nucleotide polymorphisms in estrogen synthesis pathways that are related to obesity in prepubescent girls and molecular haplotyping measurements to evaluate gene–environment interactions. Also, ways of assessing exposure to various modern environment endocrine disruptors such as phthalates and alkyl phenols through survey instruments are being developed.

Dr. Luz Claudio directs the center's COTC that focuses on providing educational materials and activities for study participants with the intent of providing benefit to the community. Collaborative links have been established with a number of community-based organizations that have expertise in providing supplemental educational materials for minority children and their families. Workshops previously held for high school girls are being modified for 7-year olds by the COTC and its collaborators.

MICHIGAN STATE UNIVERSITY

Dr. Sandra Haslam directs the center at Michigan State University, where the basic science studies will use a mouse model, and Dr. Charles Atkin from the School of Communications is leading their COTC. Their focus is on further understanding how *in utero* early postnatal and pubertal environmental exposures affect the development of the mammary gland, especially on the mechanism of progesterone in the normal mammary gland of the mouse. Their investigations have shown that the actions of two isoforms of progesterone (A and B) have different temporal effects on protein expression during development across the life span,

that these isoforms are expressed in different parts of the mammary gland, and that they differ in how they are regulated by progesterone. The importance of these findings derives from the potent mitogenic activity of progesterone in mammary carcinogenesis. A better understanding of its mechanism of action may lead to novel prevention strategies. Further work in this center will include improving our understanding of the differences between mouse and rat models in progesterone action and their specific relevance to how progesterone acts in humans. This center does not have an epidemiologic study component.

The COTC at Michigan State University was designed by faculty at the College of Communication Arts and Sciences with input from community-based breast cancer advocates. The unique health communication expertise this center offers will be important to the overall success of the network. They are assessing community concerns about the environment and breast cancer and the knowledge, beliefs, attitudes, communication behaviors, and information sources of preadolescent girls and adult women on this topic. This information will be shared within the network and will assist in the design of communication, education, and outreach strategies to be used throughout the duration of BCERC and beyond.

UNIVERSITY OF CINCINNATI

In collaboration with the Cincinnati Children's Hospital Medical Center, this BCERC site is led by Dr. Susan Heffelfinger, who also directs the basic science studies; Dr. Frank Biro directs the epidemiology study. This center is exploring how fatty acids and phytoestrogens modify estrogen synthesis, metabolism, and signaling to define mammary gland maturation and cancer initiation using a rat model. The primary hypothesis is that these dietary factors act during early childhood to determine the level of adiposity and regulate the hormonal milieu. Adiposity acting through leptin and insulin-like growth factor determines whether puberty progresses through the influence of the adrenal gland (adrenarche) or the ovaries (thelarche), the latter being associated with early menarche and subsequent risk of breast cancer. Gene expression arrays will be used to define characteristics of initiated mammary epithelial cells that can be used to examine environmental substances for their carcinogenic potential in the rat.

The epidemiologic study in girls will investigate the association of diet, adiposity, environmental factors, and psychosocial influences with the particular type of pubertal maturation (adrenache or thelarche). Comparisons will be made between girls with and without a family history of breast cancer. The goal is to recruit and retain a cohort of approximately 400 girls 7 years of age from elementary schools who will be examined semiannually to collect interview data and biospecimens that will allow measurement of hormones, growth factors, and aromatase activity as well as progression toward pubertal maturation outcomes.

The COTC in Cincinnati is lead by Dr. Kathryn Brown. The goal of the center is to work with advocates from breast cancer survivor organizations to enhance public understanding of the environmental factors that may affect breast cancer in order to inform individual decision making about environmental exposures and health practices. They also seek a public dialogue about the policy implications to the community that may arise from research findings in the center and the broader BCERC network. Multiple partners from community-based organizations are assisting the center in this work.

UNIVERSITY OF CALIFORNIA SAN FRANCISCO COMPREHENSIVE CANCER CENTER

Dr. Robert Hiatt directs the center in San Francisco, with major scientific roles played by the Kaiser Permanente Division of Research in Oakland, where Dr. Lawrence Kushi leads the epidemiologic study, and by Lawrence Berkeley National Laboratory scientists, who are collaborating with Dr. Zena Werb of UCSF on the basic science studies.

A scientific theme in the animal studies is the parallel between the steps or phases of normal mammary gland development and those associated with tumor progression, such as invasion, reinitiation of proliferation, resistance to apoptosis, and angiogenesis. Many of the genes vital to the development of the mammary gland are also associated with tumorigenesis, and many of these genes are stromally expressed. Dr. Werb and her collaborators are investigating the cross-talk between stromal and epithelial mammary cells and evaluating signals received by mammary stem cells during development. The mouse models they develop will use low-dose ionizing

radiation as a prototypical environmental stressor, but the resulting model will eventually be used for evaluating other potential environmental carcinogens suggested by the advocacy community and the human studies in girls. Findings from *in vivo* models will also be evaluated in human tissue culture systems for confirmation.

As in Cincinnati, the Bay Area BCERC is recruiting 7-year-old girls, but in this case from the membership rolls of Kaiser Permanente in the San Francisco bay area. Their goal is to recruit and retain 400 girls who were born in and are still members of the health plan and for whom birth and childhood growth records are available from the medical charts. As at the other two sites collecting information on girls as they go through puberty, the Bay Area BCERC will be gathering information on multiple environmental exposures, lifestyle factors such as dietary intake and physical activity, developmental factors such as growth history and anthropometric measures, and biospecimens for hormonal and genetic studies.

Janice Barlow of Marin Breast Cancer Watch leads the COTC for the bay area center. Her organization was one that played a key role in advocating for the centers with Dr. Olden and the NIEHS, and their role in the research of the center is particularly gratifying. Their primary aims are to integrate the principles of community-based participatory research into both of the scientific projects of the center and to create opportunities for community members, advocates, public health professionals, and policymakers to increase their understanding of the nature of the Bay Area BCERC research studies and the process of the research itself while simultaneously improving the scientist's understanding of community and environmental health concerns with regard to breast cancer.

Thus, the scientific scope and goals of these four centers are extensive, but at the same time well focused on elucidating the environmental determinants of pubertal maturation, one of the key factors known to influence a woman's risk for breast cancer. Not unexpectedly, each center differs somewhat in its particular approach to the broad research challenge, but there is also much that is similar. Efforts since the funding of the centers have been directed largely at enhancing these similarities to create standard procedures that will allow valid cross-study comparisons and pooling of data for analysis.

The BCERC Network

In the first year of the BCERCs, much time and effort was spent on standardization of experimental protocols, data collection methods and instruments, laboratory analyses, and analytic strategies. For the basic studies using animal models, this meant standardizing animal feeding and maintenance procedures, agents used for cancer initiation, approaches to gene array studies, and bioinformatic analytic strategies. More complex were the joint activities of the three epidemiologic studies, where much effort went into selecting and standardizing questionnaires, examination procedures, biospecimen collection, and analysis protocols and joint analytic strategies. Examples include the extensive questionnaire that includes sections on demographics and family history, medical history, diet, physical activity, environmental exposures, and home and cosmetic product use. Joint training to standardize questionnaire procedures and other protocols was held for representatives of the three centers that have an epidemiologic study at the University of Cincinnati in August 2004. A coordinating center at the UCSF site under the direction of Dr. Robert Hiatt has been established to coordinate questionnaire development, data entry, centralized data management, and pooled analyses. Other aspects being coordinated between centers include a website and national meetings. Also, a publications committee has been formed to set agreed procedures for the analysis of pooled data, publication tracking, authorship protocols, and other matters pertaining to publications from the network.

The COTCs have also worked together within the network even though their individual approaches to the local situation are quite varied. There has been sharing of materials and approaches where applicable, and substantial discussion of approaches to evaluation. The COTCs were responsible for coming up with a logo and the name “Early Environmental Exposures” for the overall study.

Early impressions on how well the network is functioning are largely positive. There is a substantial amount of good will between the scientists and advocates involved in the project. Efforts to involve the advocates in scientific meeting and administrative decision making are willingly undertaken and usually successful in their implementation. To be sure, there is a tension between individual site-specific goals and

obligations with those of the larger network, but this has not been a barrier to progress.

National Meetings

An activity of the centers that deserves special mention is the annual national meeting. The first, “Emerging Topics in Breast Cancer and Environment Research,” was held in Princeton, New Jersey, in November 2004 and was attended by approximately 210 scientists, advocates, guests, and program staff. The theme of this first national meeting was to highlight what is currently known about environmental influences on breast cancer. Planning for the meeting, which was a joint effort of BCERC investigators, program staff, and advocates, explicitly combined presentations of the highest scientific caliber with multiple opportunities for the advocates to learn from the presentations while providing input and having time for questions. Dr. Olden was an honored speaker at the conference and emphasized the value he places on innovative scientific thinking, interdisciplinary research, and community participation in the science.

The meeting was itself an experiment in its structure as it sought the balance between the presentation of new science and accessibility to the large number of advocates. Although many attendees were highly satisfied by the outcome, there were contrary voices from both scientists and advocates (Brenner 2004/2005) and renewed efforts to achieve the optimal balance will be needed in future years as the meetings rotate among the four centers. The 2005 annual meeting will be held in November at Michigan State University, hosted by Dr. Sandra Haslam.

Novel Opportunities

There are aspects of the BCERCs that strike me as rather unique opportunities. To be sure, they include the scientific themes made explicit in the RFA (NIEHS 2002) to gain a better understanding of the development of the normal and cancer-prone mammalian breast and of the determinants of the pubertal transition in girls through a prospective, longitudinal study. However, there is also the opportunity to put transdisciplinary science into play and the chance to evaluate a major effort at community participatory research.

Transdisciplinary science involves the integration of theoretical and methodological perspectives drawn from different disciplines to generate novel conceptual and

empirical analyses of a particular research topic (Rosenfield 1992). It differs from simple multidisciplinary or interdisciplinary science in that it seeks a true integration of existing disciplinary perspectives to create something novel and unlikely to have arisen out of discipline-specific investigations or from simply associating investigators from multiple disciplines under the loose organization of a large grant. There have been a number of efforts by the NIH to support such undertakings, including the Transdisciplinary Tobacco Use Research Centers, the Centers of Excellence in Cancer Communications, and the Center for Population Health and Health Disparities, and there have been some early efforts at evaluation (Stokols et al. 2003). However, efforts to create transdisciplinary science from teams of scientists who were not assembled for that purpose (as in the BCERCs) are unusual. This will require concerted energy from BCERC leadership and NIH program staff to take full advantage of the opportunity.

The second unique opportunity is to evaluate the outcomes of the person power, time, and money invested in the COTCs. These are designed to follow the tenets of community-based participatory research, but do they really follow the intended path for such community involvement, and is there some way to actually measure the net benefit to science, to the community, or to the goodwill created between scientists and communities derived from COTC efforts?

The Future of Centers

Finally, although the BCERCs are still in their infancy, a comment about the value of center grants in the advancement of science can be made. It should be clear that the scientific undertaking described in this article is highly interdisciplinary and draws on fields as diverse as genetics, developmental biology, computational biology, toxicology, nutritional science, epidemiology, sociology, and communications. To realize Dr. Olden's vision for "thinking outside the box" and seeking ways to create truly interdisciplinary, even transdisciplinary, science, it is difficult to see how this can be supported if not through infrastructure made possible by center grants. Many have argued that we have entered the era of large-scale science (Institute of Medicine 2003) where advances depend on collaborations, many rather sizable, in order to organize the disciplinary skills necessary to study complex problems. This cannot be done solely with traditional individual investigator-initiated grant

awards. Center grants should not replace individual investigator-initiated science, but they must remain part of any major funding agency's repertoire of support mechanisms. In the BCERCs the individual investigators are clearly going to do excellent research in their own fields, but we are also poised to create new knowledge at the intersection of disciplines that could not have occurred without the structure that has been built.

Conclusion

The BCERCs are "off and running" and are likely to contribute new discoveries because of their unique focus on the determinants of pubertal maturation, the interaction of laboratory and population science, and the role of community advocates in the scientific process. These centers would not have happened without the vision and energy of Dr. Kenneth Olden. His willingness to listen, enthusiasm for innovation, and persistence made these centers a reality. It now remains for the scientists and advocates who have come together in these centers to realize his vision and make a lasting contribution to the understanding of the role of the environment on breast cancer and eventually to more successful means for its prevention.

SUMMARY

The Breast Cancer and the Environment Research Centers (BCERCs) are a national network of four centers of excellence supported by the National Institute of Environmental Health Sciences and National Cancer Institute over a 7-year period to better understand the impact of the environment on breast cancer etiology. The scientific focus is on the determinants of pubertal maturation in young girls and the biologic mechanisms of breast development and maturation across the life span in rodent models. The centers are a unique blend of innovative, interdisciplinary science with community participation and the integration of advocates into the scientific projects. Dr. Kenneth Olden's role in the development of these centers, as well as his uncommon vision, persistence, and humanity in championing their mission, stands as a tribute to his unique contributions as a scientist, leader, and public servant.

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