Breast Cancer Takes Center Stage

Breast cancer is the second leading cause of cancer deaths in American women today, claiming more than 40,000 lives annually. Accumulating evidence suggests that interactions between genetic and environmental factors may be at the center of its causation. Understanding exactly which such factors are involved in breast cancer and their mechanisms of action is a subject of great interest among patient advocates and scientists. To help build the underpinnings of this understanding, the NIEHS and the National Cancer Institute (NCI) have jointly funded the development of four new Breast Cancer and the Environment Research Centers.

The idea for the centers arose in part from debate at a one-day brainstorming session held in April 2002, where patient advocates, breast cancer specialists, and scientists from other disciplines discussed with NIEHS staff gaps in knowledge, roadblocks to progress, and opportunities for future research regarding breast cancer and the environment. NIEHS staff used these recommendations in planning a new multidisciplinary research program.

In October 2003 came the announcement that $35 million (over seven years) had been allocated for the new centers. The four centers are located at Fox Chase Cancer Center in Philadelphia, Pennsylvania; Michigan State University in East Lansing; the University of Cincinnati in Ohio; and the University of California, San Francisco (the "Bay Area Center").

The spirit of collaboration and responsiveness to public health concerns has been fundamental in the creation of the centers. Kenneth Olden, director of the NIEHS, remarked at a November 2003 kickoff and planning meeting that "the community of breast cancer advocates were there from the inception of this idea, and we have worked [together] to make it a reality."

The research to be conducted by the centers will revolve around the hypothesis that there are periods of vulnerability in the development of the mammary gland when exposures to environmental agents may impact the breast in ways that can influence breast cancer risk in adulthood. The new centers will address this scenario by functioning as a consortium, working in close collaboration to pursue two specific approaches to this hypothesis. One approach will use basic science techniques in laboratory animals and cell cultures, and the other will use epidemiologic studies in human populations. "The four centers will work in close cooperation, so that we can do more than what could be achieved by the individual laboratories," says Gwen Collman, chief of the NIEHS Susceptibility and Population Health Branch and program administrator for the centers.

One unusual feature of the program is that the awards will be made for seven years, compared to the usual five years for center grants. This will allow for prospective studies of developmental landmarks in populations of girls, and integration of laboratory and epidemiologic research.

Michael Gushock

Research on Mammary Gland Development

The goal of the laboratory research project is to conduct collaborative experiments using animal and cell culture models to characterize the molecular basis of the mammary gland over the life span, and to determine how this development may be affected by exposure to environmental agents. Each of the four centers bring to the table unique capabilities with regard to studying a variety of animal and cell culture models to look at histologic, pathologic, cellular, and subcellular end points that may be caused by environmental exposures.

The Fox Chase Cancer Center researchers will examine the effects of exposures to hormonally active xenobiotics including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, bisphenol A, butyl benzyl phthalate, genistein, and diethylstilbestrol on the mammary gland in rats at certain periods of development. Serum from exposed rats will be analyzed to identify biomarkers of exposure to these chemicals that could possibly be used for exposure assessment in human populations. In addition, the Fox Chase team will explore how timing of exposure to these xenobiotics alters susceptibility to 7,12-dimethylbenz[*a*]anthracene, a mammary cancer inducer.

The University of Cincinnati team will use the rat as a model to study how factors related to obesity and dietary factors may interact to promote breast cancer. They will explore the effects of dietary fatty acids (such as mono- and polyunsaturated fatty acids) and phytoestrogens (such as those found in soy products) on hormonal balance, mammary gland morphology, gene expression, and susceptibility to carcinogenesis. In addition to these *in vivo* experiments, the Cincinnati team will use rat mammary epithelial organoids in culture to study mechanisms of DNA damage.

The Bay Area Center investigators will use mouse models to study the molecular basis of mammary gland development. They will expose both normal mice and those that are genetically susceptible to developing tumors to prototypical carcinogens such as ionizing radiation at different developmental points in order to define the morphologic and functional alterations that occur in the mammary gland. These experiments will be complemented with *in vitro* studies to search for cellular mechanisms of action.

The Michigan State University team will use mouse models to study progesterone receptor function and activity in the development of the breast, and how that function is altered with exposure to environmental agents. Their experiments will center around the hypothesis that increased lifetime exposure to progesterone and estrogen underlies the increased risk of breast cancer associated with early onset of menarche, late age at menopause, and hormone replacement therapy.

The centers will also participate in a coordinated epidemiologic study of the environmental and genetic determinants of puberty. This research will be conducted by prospectively following several cohorts of prepubescent girls at different stages in development to determine how hormonal changes, obesity, diet, family history, psychosocial stressors, environmental exposures, and genetic polymorphisms, among other factors, may interact to control mammary gland development and other landmarks of puberty. As a result of information provided from the animal studies, relevent human genetic polymorphisms will be selected. Then interactions between environmental agents and the genes that affect their susceptibility will be explored.

Community Outreach and Translation

The work of the centers will be enhanced and their discoveries transmitted to the public through the Community Outreach and Translation Core (COTC) in each center. The COTCs will provide an essential link between the scientists and the communities that are likely to benefit from the information being generated by the research.

The COTCs will focus their efforts on working with area breast cancer advocacy groups and other local organizations to reach the communities that will eventually participate in the studies. The centers will work closely with their community partners to translate the findings, as they are uncovered, into useful, pertinent health messages that can engage potential participants in the studies in such a way that they become invested in the progress of the studies, and

Breast Cancer and the Environment Research Centers

Center	Collaborators	Community Partners
University of California, San Francisco San Francisco, California	Marin Breast Cancer Watch Lawrence Berkeley National Laboratory University of Michigan Kaiser Permanente of Northern California Roswell Park Cancer Center California Department of Health Services Marin County Department of Health and Human Services	Marin Breast Cancer Watch Bayview Hunters Point Health & Environmental Assessment Task Force Breast Cancer Fund Bay Area Breast Cancer SPORE Advocacy Core Community Health Academy
Fox Chase Cancer Center Philadelphia, Pennsylvania	The University of Alabama Mount Sinai School of Medicine	The Renaissance University for Community Education of the Harlem Children's Zone Project Girls, Inc. New York City Parks Foundation Community Science Specialists Share
University of Cincinnati Cincinnati, Ohio	Cincinnati Children's Hospital Medical Center	Breast Cancer Alliance of Greater Cincinnati Patterns, Inc. Pink Ribbon Girls Susan G. Komen Breast Cancer Foundation, Greater Cincinnati Affiliate American Cancer Society, Cincinnati Area Office Breast and Cervical Cancer Screening Project Greater Cincinnati Occupational Health Center Lower Price Hill Women's Wellness Group National Breast Cancer Coalition The Wellness Community YWCA Breast & Cervical Health Network
Michigan State University East Lansing, Michigan	n/a	Faith Access to Community Economic Development Susan G. Komen Breast Cancer Foundation Michigan Environmental Council American Cancer Society, Great Lakes Division

retention is thus enhanced. This will be especially important given the expected length of the studies.

In addition, the Department of Communication at Michigan State University will create public health message materials that can be used in the mass media nationwide. Communication of health messages will be a crucial part of the studies; it must strike a balance between the awareness of potential risk factors and health-promoting messages. Says Maria Carolina Hinestrosa, cofounder and executive director of the patient advocacy organization Nueva Vida, "We must avoid promoting fear of the breast, where girls and young women see their breasts as a threat."

Mechanisms for Collaboration

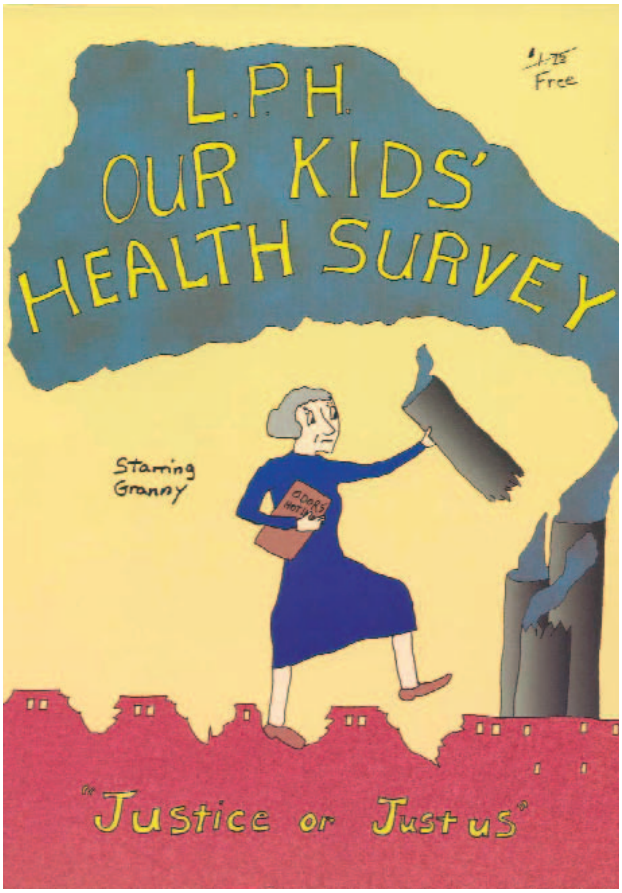
The centers program was created through a cooperative agreement that will support the work to be conducted both within and across centers. A steering committee will govern the network, and will comprise the center directors, a COTC member from each center, two NIEHS representatives, and one NCI representative. The steering committee will establish specific research tasks and milestones for each project. The committee will also oversee subcommittees for each of the two projects.

The progress and activities of the centers will be reviewed by a council working group, which will advise the NIEHS director on that progress and make recommendations for complementing this work. The working group has been established as a subcommittee of the National Advisory Environmental Health Sciences Council (which advises the U.S. Department of Health and Human Services, the NIH, and the NIEHS on research issues, programmatic content, and related factors in the environment that affect human health). It is composed of two of that council's members, one member of the NCI National Cancer Advisory Board, and six ad hoc members

beyond the BENCH

Keeping It Close to Home with imby

"imby"—which stands for "in my back yard"—is a community health and environment research center in the University of Cincinnati Department of Environmental Health. It was founded in 1999 in response to the request voiced by residents, environmental advocates, and community-based organizations at a prior NIEHS Town Meeting for a better understanding of research methods and greater access to study findings. Launched with funding from the department and the NIEHS Center for Environmental Genetics at the university, imby's mission is to build community partnerships to assess, address, and improve environmental and public health issues through access to resources, effective strategizing, capacity building, advocacy, research, and analysis and interpretation of data.



The "back yard" served by imby includes various neighborhoods in Cincinnati. The center partners with the Urban Appalachian Council on an NIEHS Environmental Justice: Partnerships for Communication grant that provided technical expertise for the design, conduct, and analysis of two community-based participatory research projects in the Lower Price Hill (LPH) neighborhood. The first was the LPH Children's Health Survey. Members of the LPH Environmental Leadership Group (a group of community residents organized around environmental health issues) were trained in survey research methods including survey design, randomization, recruitment and interview techniques, quality control, and confidentiality procedures. Neighborhood residents have created and published a comic book to communicate results of the survey to area residents. Community educational programs are being developed to address the significant findings of the survey in areas such as lead poisoning, asthma, ear infections, and smoking cessation. In another project, imby is now working with the LPH Environmental Leadership Group and the Urban Appalachian Council on an LPH Women's Health Survey. This questionnaire was translated into Spanish so area Latinas could participate in the survey.

imby has also partnered with the Fernald Community Health Effects Committee (F-CHEC). F-CHEC is a grassroots organization of residents living around a former uranium enrichment facility that was shut down by the Department of Energy in 1989. Citizens concerned about the potential impact of the Fernald site on the health of area residents as well as current and former workers formed F-CHEC in 2002 when the Centers for

imby

representing breast cancer advocates and other breast cancer researchers. The working group will help produce messages to be shared with the breast cancer community.

Collaborators in the centers hope that the findings that arise from their efforts will translate into applications that increase awareness of the causes of breast cancer and their implications for public health. In the words of NCI epidemiologists Sandra Melnick and Deborah Winn, speaking at the November 2003 kickoff meeting, these centers will allow scientists to ask the "right questions with the right technology, and provide answers [on the causes of breast cancer] to the public." **–Luz Claudio**

Disease Control and Prevention disbanded the Fernald Health Effects Subcommittee. imby provides training and technical expertise to F-CHEC and also collaborated with F-CHEC to prepare a grant proposal to the Citizens' Monitoring and Technical Assessment Fund.

The resulting project, titled "Fernald Area Cisterns and Wells: What Is Known and What Does the Public Need to Know?," includes a survey of area residents to determine the historical and present-day uses and maintenance patterns of residential cisterns. The questionnaire will provide important information about cistern water as a possible route of exposure for Fernald area residents to radiological, chemical, and heavy metal contaminants.

imby has worked with community residents in neighborhoods outside Cincinnati as well, including Jesus People Against Pollution (JPAP), a grassroots organization in Columbia, Missouri. JPAP had file drawers full of questionnaires that had been completed by area residents in a project to characterize people's exposure to and possible health effects from explosions at a nearby Superfund site. imby worked with JPAP to organize the surveys, develop a data entry program, and train residents to use it so that the survey results could be analyzed.

imby will also play a role in the recently funded NIEHS Breast Cancer and the Environment Research Center at the University of Cincinnati and Cincinnati Children's Hospital Medical Center. For more information on imby projects, visit the program's website at **http://www.eh.uc.edu/imby/**. **–Kimberly G. Thigpen and Kathryn M. Brown**

Headliners | Respiratory Disease

NIEHS-Supported Research

Image Source

Low-Level Ozone, Particulate Matter, and Children with Asthma

Gent JF, Triche EW, Holford TR, Belanger K, Bracken MB, Beckett WS, Leaderer BP. 2003. Association of low-level ozone and fine particles with respiratory symptoms in children with asthma. JAMA 290:1859–1867.

Many studies have shown that children with asthma are particularly vulnerable to adverse health effects from exposure to high levels of ambient ozone and particulate matter. These studies have shown that children with asthma living in areas that regularly experience periods of high levels of these pollutants are at significant risk for respiratory symptoms, decreases in lung function, and the need for asthma medication such as rescue inhalers. But results from other epidemiologic studies of children with asthma living in regions with levels of pollution within or near compliance with Environmental Protection Agency (EPA) standards suggest that even these standards may not protect this more vulnerable group. The current study, conducted by NIEHS grantees Brian P. Leaderer of the Yale University School of Medicine and William S. Beckett of the University of Rochester School of Medicine and Dentistry in New York, examines the simultaneous effects of ozone and particulate matter at levels below EPA standards on daily respiratory symptoms and rescue medication use among children with asthma.

The researchers examined 271 children from a cohort of families living in New England who were participating in a study of asthma development. For each child, the team recorded demographic information, a medical history, daily respiratory symptoms (wheeze, persistent cough, chest tightness, and shortness of breath), and medication use (maintenance medications including inhaled and systemic steroids and leukotriene inhibitors, and rescue medications including bronchodilators). Air quality assessments over the 183-day sampling period were obtained from state departments of environmental protection.

For ozone, same-day concentrations above a 1-hour average of 63.3 parts per billion and an 8-hour average of 51.6 parts per billion were significantly associated with respiratory symptoms and rescue medication use among children with asthma severe enough to require using maintenance medication. These concentrations are significantly lower than the EPA standards of 120 and 80 parts per billion, respectively. Levels of particulate matter were not associated with any outcome in children with asthma, and no exposure-dependent associations were observed for any outcome with either pollutant among children who were not using maintenance medication.

The finding that asthmatic children are particularly vulnerable to ozone at levels below current EPA standards has major public health implications. On days when the ozone level is considered safe for the general population, this at-risk group may need to take additional precautions. Parents and physicians need to be aware of ozone alert forecasts and may need to take measures to limit outdoor activity for children with asthma on days when ozone is elevated but still below accepted standards. **–Jerry Phelps**