

Centered on Breast Cancer

A relationship between early menarche in girls and later development of breast cancer has long been observed. Some environmental factors, such as diet and exposure to endocrine disruptors and other chemicals, could affect children's timing and pace of puberty and development. This leads to the question of whether exposure to these agents may also lead to breast cancer later in life. That is the scientific premise for the establishment of the Breast Cancer and the Environment Research Centers (BCERCs), which presented results of ongoing studies at their third annual meeting on 2–3 November 2006.

The centers are co-funded by the NIEHS and the National Cancer Institute (NCI) Epidemiology and Genetics Research Program. They work together to integrate community outreach and two lines of research: 1) basic biology of the mammary gland and its development using animal models, and 2) epidemiological studies of how environmental factors affect puberty in girls. Four centers were established across the nation: the Fox Chase Cancer Center in Philadelphia (collaborating with Mount Sinai School of Medicine in New York and the University of Alabama at Birmingham), the University of Cincinnati in Ohio (collaborating with Cincinnati Children's Hospital Medical Center), the University of California, San Francisco (collaborating with numerous partners including Lawrence Berkeley National Laboratory), and Michigan State University in East Lansing.

"Using a transdisciplinary scientific approach, the centers are able to investigate possible windows of susceptibility during pubertal development more comprehensively and on a larger scale," said Shannon Lynch, a program analyst at the NCI. The BCERCs' ability to work closely together, share resources, compare findings, and establish common research protocols is especially important in epidemiological studies. With each center recruiting a number of girls from diverse racial/ethnic, geographical, and socioeconomic

backgrounds, the data that are ultimately generated should be more robust due to a greater number of samples that are more representative of different populations.

Research Update

One example of the kind of multidisciplinary data that can be generated by this collaboration can be found in a paper presented at the meeting, which was later published in the January 2007 issue of *EHP*. Center researchers collaborated with the CDC to analyze urine samples collected from 6- to 8-year-old girls to assess the levels of biomarkers of exposure to a number of phytoestrogens, phthalates, and phenols. Many of



Window to the future. The Breast Cancer and the Environment Research Centers are looking at ways that early environmental exposures may influence later breast cancer risk.

these compounds are known or suspected to cause endocrine disruption.

The authors found that these potentially hormonally active compounds were widely detectable in the girls studied. For several of the compounds, concentrations varied by geographic location, body size, or race/ethnicity such that meaningful comparisons may become possible. It is still too early to tell whether exposure to these compounds will be associated with puberty, but so far the preliminary data show that exposures can be substantial and perhaps biologically relevant.

Each center is also producing new research results within its own populations of study. The University of California center, for example, working together with the Kaiser Permanente Division of Research, has recruited 444 girls, along with their

families, to study how environmental exposures may affect growth and development. The study participants are members of Kaiser Permanente of Northern California, an integrated prepaid health care system, so researchers have access to early medical information for the girls including birthweight.

In preliminary analyses, Larry Kushi, associate director of the Kaiser Permanente Division of Research, and colleagues found that higher birthweight predicted risk of overweight in 6- to 7-year-old girls. It is important to assess peripubertal obesity in girls enrolled in the study because obesity is a strong predictor of breast development;

how obesity may affect timing and degree of puberty development is one of the subjects of this investigation. A significant proportion (29%) of girls enrolled in this study were classified as overweight, defined as being at or above the 85th percentile for body mass index. Ongoing analyses are assessing the levels of pubertal development in the cohort. The preliminary findings suggest that the black and Latina girls are having a higher prevalence of early puberty onset.

Investigators at the meeting also presented results of studies conducted in the basic science components of their centers. Deborah J. Clegg, an assistant professor in the Department of Psychiatry at the University of

Cincinnati College of Medicine, conducted a yet-unpublished study to assess how caloric content and type of dietary fat eaten may affect obesity and carcinogenesis susceptibility in laboratory rats. Her team tested high- and low-fat diets rich in olive oil, fish oil, safflower oil, or butter (a "1950s diet"). They found that the high-fat olive oil diet accelerated puberty and increased propensity to carcinogenesis in the exposed rats. Additionally, they found that the high-fat diets enriched with safflower oil and fish oil increased body weight and susceptibility to carcinogenesis. Interestingly, however, the high-fat butter diet did not increase body weight or carcinogenicity.

Defining Messages

In addition to the basic and epidemiological research being conducted, each center

also has a Community Outreach and Translation Core (COTC). The COTCs have different functions within each center, including sharing information with the community, conducting research on translating science findings, and studying recruitment and retention strategies.

The COTC at Michigan State University presented data on the types of meaningful messages about breast cancer that women remember for long periods of time and the sources of such messages. Based on responses from 137 women who completed an online questionnaire, researchers concluded that most messages were recalled from the mass media. Most messages were about the detection of breast cancer rather than its prevention. These findings demonstrate that the media has a strong influence on the messages received by women, perhaps more influence than the medical community.

The issue of what health messages can impact the community at large resonated with many participants present at the meeting, which included leaders of the breast cancer control advocacy community, who are active participants in the centers. Beth Hartung, a member of the Young Survival Coalition (a network of breast cancer survivors who are 40 or younger), expressed this succinctly as she asked a panel of center scientists, "What do we tell our daughters [about their risk of breast cancer]?" Program administrator Les Reinlib of the NIEHS Division of Extramural Research and Training, himself the father of two daughters and husband to a breast cancer survivor, answered, "We tell them to make lifestyle choices that improve general health."

For now, until more definitive research on specific environmental exposures has been completed, exercise and good nutrition are the two main lifestyle choices that can help in the prevention of disease. And despite the uncertainty that remains, there have been many scientific advances that have extended the lives of women diagnosed with breast cancer.

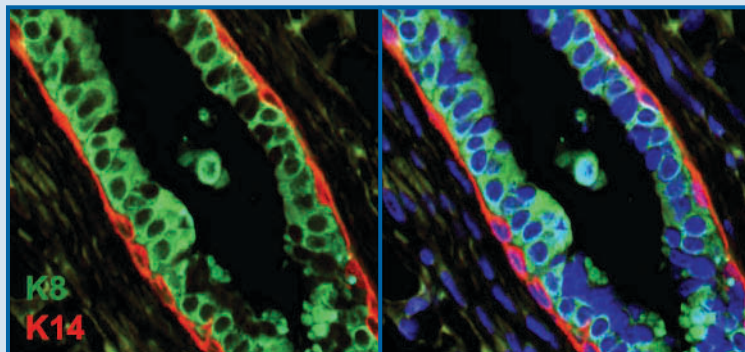
Andrea Ice, cofounder of the Sisters Network (a national breast cancer survivorship organization for black women), has seen this first-hand. "Since my initial diagnosis in 1989, the biggest change has been that women see other women who have survived the disease for many years," she says. "It is no longer a death sentence." The hope is that the BCERCs will be able to add prevention to the progress made in breast cancer research.

—Luz Claudio

Headliners

NIEHS-Supported Research

Breast Cancer



Loss of *GATA-3* leads to expansion of undifferentiated luminal cell population

GATA-3 Maintains Differentiation of Mammary Ductal Cells

Kouros-Mehr H, Slorach EM, Sternlicht MD, Werb Z. 2006. *GATA-3* maintains the differentiation of the luminal cell fate in the mammary gland. *Cell* 127:1041–1055.

GATA-3 is one of a family of genes responsible for driving the processes that turn undifferentiated stem cells into specialized mature cells. Now NIEHS grantee Zena Werb of the University of California, San Francisco, and colleagues have determined that the *GATA-3* protein is also required for the maintenance of differentiation in ductal cells of the mammary gland. This new finding suggests that *GATA-3* may play a key role in the development of breast cancer.

Mammary ductal cells, also known as luminal cells, line the mammary ducts that carry milk during lactation. Although not much is known about the differentiation of luminal cells, they are implicated as a primary site in the mammary gland for cancers to form. Cancer researchers know that breast tumors with high *GATA-3* expression have a good prognosis. These cancers tend to be well-differentiated, and the cells maintain many characteristics of normal mammary cells, including high numbers of estrogen receptors. However, cancers with low expression of the protein tend to be diffuse and poorly differentiated, and lead to poor prognosis for the patient.

Upon devising a microarray strategy to identify novel regulators of mammary development, the investigators observed the mammary epithelium *in vivo* of laboratory mice genetically altered to lack *GATA-3*. They found that mature cells reverted to the less specialized, undifferentiated state, which is characteristic of aggressive cancer cells. The research team also found *GATA-3* in all mammary duct luminal cells in normal mice at puberty and into adulthood.

The results suggest that the loss of functioning genes and the subsequent failure to maintain the mature state of the cells is what leads to the loss of differentiation and uncontrollable proliferation during cancer progression. Prior to this finding, it was unclear that maintaining differentiation of mammary cells was an active process and that the *GATA-3* protein was responsible for that maintenance. The team is now studying how *GATA-3* controls cell fate and its role in breast cancer. This research could also have implications in other cancer types. —Jerry Phelps

BEYOND THE BENCH

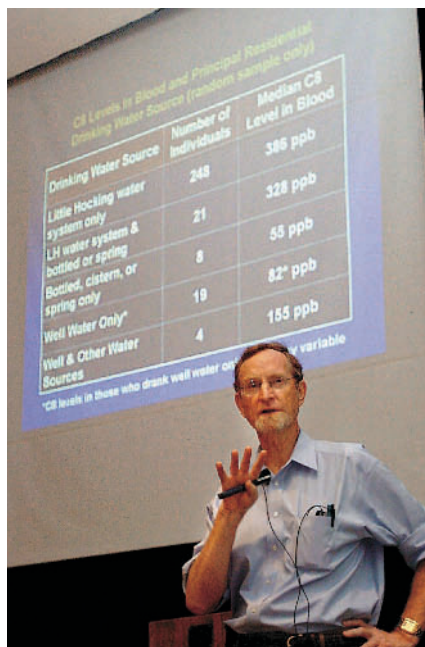
Research Helps Clean Up A Water Supply

Many of the conveniences of modern life are made possible with man-made compounds. One such chemical, perfluorooctanoic acid (PFOA), has a broad spectrum of use, from the manufacture of non-stick cookware to aerospace technology. PFOA's persistence in the environment is troubling, especially given studies demonstrating that exposure to the compound can cause developmental delays and cancer in lab animals. Thus, when PFOA was detected in the water supply of Little Hocking, a village located across the Ohio River from and downwind of a Washington, West Virginia, fluoropolymer manufacturing facility, researchers at the University of Pennsylvania NIEHS Center of Excellence in Environmental Toxicology (CEET) felt compelled to investigate. The contamination was first reported to Hong Zhang, a local doctor enrolled in a practicum residency for physicians in occupational and environmental medicine at the university.

According to CEET deputy director Edward Emmett, who also directs the center's Community Outreach and Education Core, the research team's immediate focus was on determining whether, how, and to what extent Little Hocking residents were being exposed to PFOA. The CEET investigators joined with community partners Grand Central Family Medicine in Parkersburg, West Virginia, and the Decatur Community Association in Cutler, Ohio, to design a study, recruit study participants, and collect data. The group applied for and received an environmental justice grant from the NIEHS, and began work in July 2004.

The investigators distributed questionnaires to a random sampling of residents who used either private or public drinking water sources, and examined blood serum samples to assess PFOA concentrations. PFOA water concentrations were obtained from the Ohio EPA. Levels averaged 3.55 ng/mL in 2002–2005, some of the highest ever reported in public water supplies in the United States.

Overall, blood serum analysis showed that the residents' levels were 60–75 times higher than in the general U.S. population. The investigators found that serum PFOA was especially high in those who ate more home-grown fruits and vegetables. Emmett says it is unclear if this was due to PFOA



Town meeting. Edward Emmett presents results of the CEET's findings to the Little Hocking community.

making its way into the fruits and vegetables themselves, or to PFOA in water used for cooking, canning, and cleaning.

An air dispersion model based on estimated emissions from the Washington plant revealed that serum PFOA levels were no different for those people living in areas with higher air concentrations than for those living where there was minimal PFOA in the air. Regardless of location, higher concentrations were found in young children and older adults, as well as in people who worked directly with PFOA in production areas of the Washington plant (all three groups' serum levels were almost twice as high as other residents accessing the Little Hocking water supply).

The research team examined all blood samples for biomarkers indicating DNA damage, but found no sign of adverse health effects. However, given what is known about the chemical's effects in lab animals, Emmett says that lowering the Little Hocking residents' exposure was prudent, and the independent research conducted by the partnership helped empower the community to secure a cleaner drinking water supply. "What has been so compelling and gratifying about this work has been witnessing how powerful credible, nonbiased information collected without conflict of interest can be in altering peoples' behavior voluntarily," says Emmett.

The Washington plant began offering bottled water to all residents being serviced

in the Little Hocking Water District within days of an October 2005 community meeting where study results were presented. Other findings from the study suggested that carbon filters in the home could help to remove some PFOA from the water. Still, these were not considered viable long-term solutions, so a new filtration facility is being created to remove all PFOA from the water supply. The facility should be functioning in a few months.

Emmett says it is also gratifying to know that the partnership's research has had a positive impact on the community. One resident remarked, "There was a large fine from EPA. There was a lawsuit, and a lot of money changed hands. But it's [the CEET] study that has changed the water I drink."

The study, which won first prize in the May 2006 EPA Science Forum, was described in two articles in the August 2006 *Journal of Occupational and Environmental Medicine*. A follow-up study is now under way to measure community members' current PFOA blood levels. More information is available at <http://lhwc8study.org/>.

—Tanya Tillett