NIEHS
National Institute of Environmental Health Sciences

Environmental Factors and Breast Cancer Risk

For millions of women whose lives have been affected by breast cancer, the 1994 discovery of the first breast cancer gene by researchers from the National Institute of Environmental Health Sciences (NIEHS) was a welcome sign of progress in the fight against this dreaded disease. While this discovery and others like it are certainly encouraging, statistics tell us that breast cancer is still a major health concern for women everywhere. According to the American Cancer Society, more women in the United States are living with breast cancer than with any other non-skin cancer. Breast cancer is the leading cause of cancer death for U.S. women between the ages of 20 and 59, and the leading cause of cancer death for women worldwide.

Gene-Environment Interactions

For years, NIEHS has played a leadership role in funding and conducting studies on the ways in which environmental exposures increase breast cancer risk. These studies have included the use of animal models to understand the role of environmental agents in the initiation and progression of cancer, as well as research on chemical risk factors and genetic susceptibility in human populations.

Although scientists have identified many risk factors that increase a woman's chances of developing breast cancer, they do not yet know how these risk factors work together to cause normal cells to become cancerous. Most experts agree that breast cancer is caused by a combination of genetic, hormonal and environmental factors.

The Sister Study

As new research continues to unravel the mysteries surrounding the causes of breast cancer, NIEHS scientists are laying the groundwork for a landmark study of the possible interplay between genetics and the environment in the development of this disease. The Sister Study is enrolling 50,000 healthy sisters of women diagnosed with breast cancer from across the country. Women of all backgrounds and ethnic groups who are between 35 and 74 years of age are encouraged to participate.

Sisters of breast cancer patients share many of the same genes, are more likely to develop the disease themselves, and are likely to have been exposed to the same environmental risk factors during early childhood.

The researchers will compare the genetic profiles and environmental exposures of sisters who don't develop breast cancer with those who do become cancer patients in order to uncover clues that may ultimately eliminate this dreaded disease.

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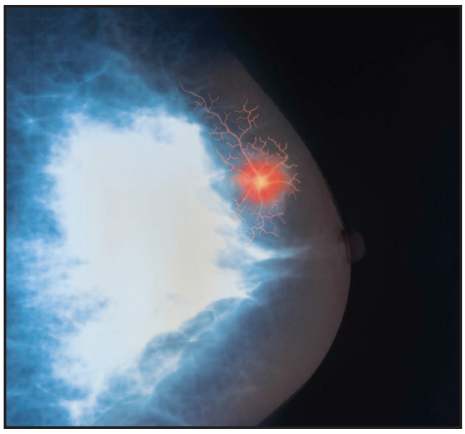
Study volunteers provide researchers with samples of their blood, urine, toenail clippings and household dust, each of which will be analyzed for pesticides, heavy metals and other environmental chemicals that may be linked to breast cancer development. The researchers will also look for specific gene variations that may predispose a woman to the effects of cancer-causing agents. Women enrolled in the study also fill out detailed questionnaires about their health history, past environmental exposures, and lifestyle. The participants will be given yearly follow-up questionnaires to account for changes in their health status or environmental exposures.



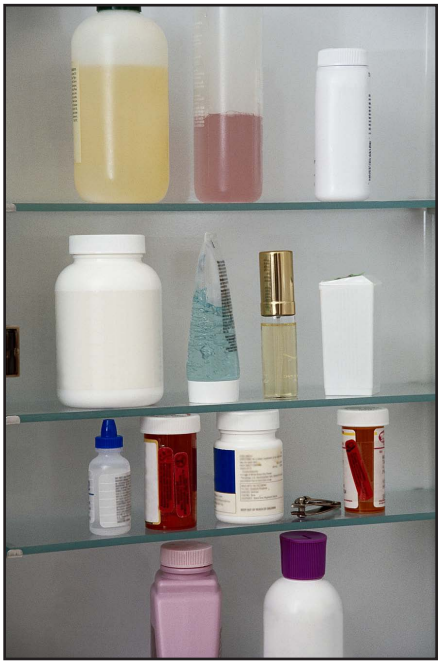
Discovery of the BRCA1 Gene

The impact of family history on breast cancer risk suggests that genetic factors play an important role in breast cancer susceptibility. Researchers are just beginning to understand how changes in certain genes can impair the gene's ability to control cell growth and division, causing normal breast cells to become cancerous. In 1994, NIEHS scientists collaborated with researchers from the University of Utah Medical Center to identify a gene called BRCA1 that, when defective, can predispose a woman to hereditary breast and ovarian cancer.[1] Diagnostic tests can now identify women who have inherited defective copies of the gene and are more likely to develop breast cancer.

Although genetics is an important contributor to breast cancer development, twin studies conducted by scientists in Scandinavia showed that inherited factors accounted for only 27 percent of breast cancer risk.[2] Another study shows that the breast cancer rates of descendants of Japanese women who migrate to the United States become similar to the higher breast cancer rates of Western women within one or two generations.[3] These findings point to the significant role played by environmental factors in determining breast cancer susceptibility.

Cancer-Causing Chemicals

Scientists are particularly interested in whether exposure to naturally occurring and synthetic chemicals may influence breast cancer risk. This includes exposure to chemicals in the air we breathe, the food and beverages we consume, and the chemicals that come in contact with our skin. The National Toxicology Program, an interagency testing program headquartered at the NIEHS, has listed more than 40 chemicals in its Report on Carcinogens because they were found to cause tumors in laboratory animals. These include pharmaceutical products such as diethylstilbestrol, a synthetic form of estrogen that was used to prevent miscarriages, chemical



solvents and flame retardants, and a variety of chemicals used in the manufacturing of dyes, rubber, vinyl, and polyurethane foams.

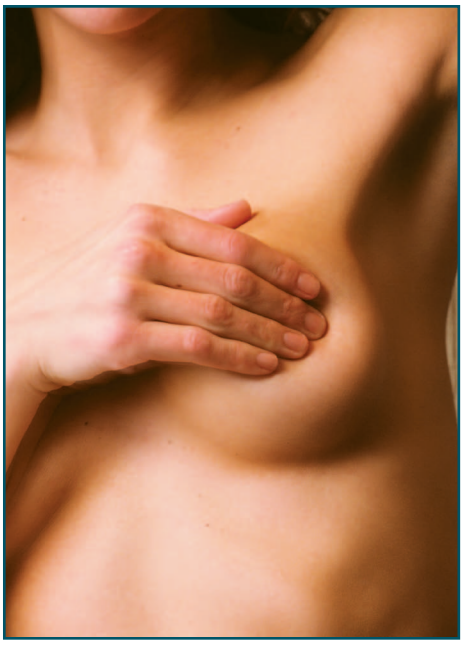
Breast Cancer and Environment Research Centers

Recent studies suggest that exposures to cancer-causing chemicals during development may affect breast cancer risk later in life. During early childhood and adolescence, the developing breast tissue is composed of rapidly dividing cells. These immature breast cells are much more susceptible to the damaging effects of environmental chemicals. Results from animal studies have shown that early exposures to some chemicals may keep the mammary gland in an immature state for longer periods, increasing its susceptibility to chemical insult.

In an effort to uncover the links between early environmental exposures and cancer risk, NIEHS is partnering with the National

Cancer Institute to fund four Breast Cancer and the Environment Research Centers *(see text box on last page)*. The purpose of the centers is to investigate the impact of prenatal and childhood exposures on mammary gland development, and the potential of these exposures to alter the risk of breast cancer in later adulthood. The research findings will be developed into public health messages designed to educate young women who are at risk for breast cancer about the roles of environmental agents in breast cancer development, and the importance of reducing their exposures to these agents.

Initiated in 2003, the centers have worked in close collaboration on two different approaches to the early exposure hypothesis. One approach will use basic science techniques in laboratory animals and cell cultures, while the other will use epidemiologic studies in human populations. Each center has a community outreach component to ensure that the views and concerns of the breast cancer advocacy community are heard and that the research findings are disseminated to the public.



Scientists at the University of California, San Francisco have found that GATA-3, a gene that guides the development of stem cells into mature mammary cells, is also required for mammary cells to remain in the mature state during adulthood. Experiments in mice reveal that without the critical gene, mature mammary cells revert to a less specialized state that is characteristic of aggressive breast cancer.[4] The results suggest that a defective GATA-3 gene may play a significant role in the development of certain kinds of breast cancer.

At the University of Cincinnati Center, investigators are studying the effect of childhood diet and obesity on the maturation of the developing mammary gland and subsequent risk of cancer later in life. Their preliminary work with animals shows that treatment with soy and other estrogen-like plant compounds may influence not only the rate of mammary gland maturation, but also the susceptibility of the gland to chemical carcinogens. They are also testing the hypothesis that pre-pubertal obesity in young girls may lead to earlier first menstruation and increased susceptibility of the mammary gland to carcinogenic insults.

Researchers at Fox Chase Cancer Center are exposing rats to the plasticizers bisphenol A and butyl benzyl phthalate at different times during mammary gland development. The investigators are finding that these endocrine disrupting compounds activate different genes depending on the time of the exposure and the age at which the rats are examined.

Experiments conducted by scientists at Michigan State University are focusing on the role of progesterone, a hormone secreted in the second half of the menstrual cycle, in breast cancer development. The researchers are using animal models to study the influence of progesterone on mammary gland cell growth and maturation. The responses they get from the animal data may shed new light on the role of this female hormone in human breast development.

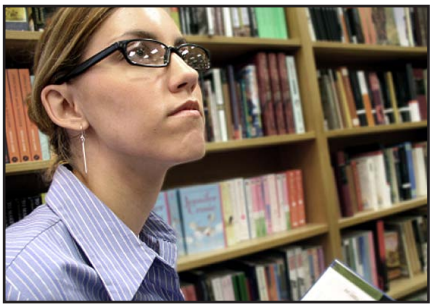
Chemical Exposures in Human Populations

In some regions of the country, where there is an unusually high incidence of breast cancer, environmental factors have been targeted as a possible cause for this increase. During the 1990's, the NIEHS and the National Cancer Institute co-funded the Long Island Breast Cancer Study Project, one of the largest and most comprehensive studies ever conducted on the environmental

causes of breast cancer, to investigate the high rate of breast cancer on Long Island in New York.

The study scientists focused their investigation on three widespread pollutants to which many of the Long Island residents had been exposed – organochlorine pesticides, including DDT and its metabolite DDE, polychlorinated biphenyls, toxic compounds used in electrical transformers, and polycyclic aromatic hydrocarbons (PAHs), a primary component of urban air pollution. Although there was some evidence of a modest increase in the risk of breast cancer from PAH exposure, the researchers did not identify any environmental factors that could be responsible for the high incidence of breast cancer in the Long Island area.[5] In a separate study conducted on Long Island women, researchers at Stony Brook University found no association between exposure to electromagnetic fields from residential power use and breast cancer risk.[6]

A similar NIEHS-NCI funded study of environmental exposures and breast cancer incidence, the Northeast Mid-Atlantic Breast Cancer Program, included data from five separate studies – two conducted in New York, one in Connecticut, another in Maryland, and the Nurses' Health Study, a nationwide investigation into the risk factors for major chronic diseases in women. In each of the studies, blood was drawn from both breast cancer patients and healthy controls, and tested for DDT, DDE, and polychlorinated biphenyls. A combined analysis of the data from the five studies revealed no significant association between the subjects' serum concentrations of these compounds and an increased risk of breast cancer.[7]



Pursuing New Leads: Artificial Light

Results from a study conducted by NIEHS-funded researchers in New York are the first experimental evidence that artificial light may play an important role in breast cancer development. The results show that nighttime exposure to artificial light stimulated the growth of human breast tumors by suppressing the levels of a key hormone called melatonin. The study also showed that extended periods of darkness greatly slowed the growth of these tumors.(8) The results provide a possible explanation for the higher rate of breast cancer in female night shift workers and the epidemic rise in breast cancer incidence in industrialized countries like the United States.

While these findings are encouraging, more research is needed to pinpoint the environmental and genetic factors that determine breast cancer susceptibility. Once scientists can identify the elements that are associated with cancer risk, appropriate interventions and precautions can be designed for those who are most likely to develop the disease.

NIEHS Breast Cancer and the Environment Research Centers

- Fox Chase Cancer Center, Philadelphia
- University of California, San Francisco
- Michigan State University, East Lansing
- University of Cincinnati, Cincinnati, Ohio

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