NCI's Extramural Research Program on Breast Cancer and the Environment

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Abstract:

The Epidemiology and Genetics Research Program (EGRP) manages the National Cancer Institute's (NCI) grant-supported research on the etiology of breast and other cancers. Since the early 1990s, EGRP, together with the National Institute of Environmental Health Sciences (NIEHS), has funded three large-scale initiatives investigating relationships between environmental exposures and risk for breast cancer—the **New England/Middle Atlantic (NE/MA) Breast Cancer Study, Long Island Breast Cancer Study Project (LIBCSP)**, and presently, the four **Breast Cancer and the Environment Research Centers (BCERCs)**. NE/MA and the LIBCSP have played important roles in understanding reasons for the high rates of breast cancer in some regions of the country, and they have provided valuable research results that have fairly conclusively ruled out several suspected environmental agents. Now with LIBCSP data, researchers are aggressively pursuing studies of gene-environment interactions. A geographic information system for Long Island also is available that researchers are invited to use in exploring relationships between environmental exposures and breast cancer. The ongoing BCERCs focus on determinants of puberty in young girls, as well as in animal models, and the effect of environmental factors on this process. Congressional mandates for research, the emergent role of breast cancer advocates in the research process, and the research findings themselves have made and continue to make the study of breast cancer and the environment scientifically and socially unique. EGRP Web site: *epi.grants.cancer.gov.* LI GIS Web site: *www.healthgis-li.com.* *BCERC* Web site: *www.bcerc.org.*

Geographic Patterns of Breast Cancer Mortality:

In the 1990s, geographic variation in cancer incidence and mortality became a public health concern. Maps of the distribution of breast cancer mortality rates for the United States had shown a pattern of elevated rates among white females in the Mid-Atlantic, Northeast, and North Central regions, and some areas of the West. This pattern has persisted for more than four decades (DeVesa SS, 1999), although in recent years, the regional variation has diminished somewhat as rates in the South have risen (Sturgeon, 2004).

Breast cancer mortality rates by county for white females for 1970-1994 (age-adjusted to 1970 U.S. population). Source: *Atlas of Cancer Mortality in the United States: 1950-1994*. Web site: *www3.cancer.gov/atlasplus.*

As a result of observing the pattern of elevated rates, in 1992 the U.S. Congress mandated a study of factors that may contribute to breast cancer in the Northeast and Mid-Atlantic states. In response, the National Cancer Institute (NCI), in collaboration with the National Institute of Environmental Health Sciences (NIEHS), funded six studies, known collectively as the Northeast and Mid-Atlantic (NE/MA) Breast Cancer Study.

Principal Investigators	 **Jo Freudenheim, Ph.D.** University at Buffalo	 **Kathy Helzlsouer, M.D., M.H.S.** Johns Hopkins University	 **David Hunter, M.B.B.S., M.P.H., Sc.D.** Brigham and Women's Hospital/Harvard University	 **Mary Wolff, Ph.D.** Mount Sinai School of Medicine	 **Tongzhang Zheng, M.D., Sc.D.** Yale University
Major Laboratory, Epidemiologic Analyses	Organochlorines, carcinogen-metabolizing enzymes	Nutrients, organochlorines, glutathione S-transferase	Organochlorines, vitamin D, electric blankets	Organochlorines, carcinogen-metabolizing enzymes	Organochlorines in breast adipose tissue and serum

Five of the studies focused on chemical exposures, particularly organochlorine pesticides, including DDT, and polychlorinated biphenyls (PCBs). PCBs are a group of chemical compounds found in coolants and lubricants in transformers, capacitors, other electrical equipment, and some consumer products. Findings from these individual studies and from a combined analysis of pooled data from the studies did not find a link between DDT or PCBs and increased risk for breast cancer (Laden F, 2001). The sixth study focused on electromagnetic fields (EMFs) and also is part of the Long Island Breast Cancer Study Project (LIBCSP). Additional NE/MA information: *epi.grants.cancer.gov/ResPort/NEMAbcs.html*.

Long Island Breast Cancer Study Project

Mortality patterns for breast cancer in the United States also prompted interest and concern among residents of Nassau and Suffolk counties (Long Island), New York. Breast cancer advocates sought their Congressional representatives' assistance and, in 1993, a Public Law was enacted directing NCI, in collaboration with NIEHS, to investigate environmental exposures and other factors that may be responsible for the elevated breast cancer rates in the two Long Island counties and in Schoharie County, New York, and Tolland County, Connecticut, two counties that at one time had the highest age-adjusted mortality rates for breast cancer.

The Long Island Breast Cancer Study Project (LIBCSP) was established in response. It consists of more than 10 projects that include epidemiologic studies, establishment of the Metropolitan New York Registry of Breast Cancer Families, laboratory research on mechanisms of action and susceptibility in the development of breast cancer, and the development of a geographic information system (GIS). Most of the research is completed, and findings on the main hypotheses have been published.


Marilie Gammon, M.D.


M. Cristina Leske, M.D., M.P.H.

The centerpiece study is a population-based, case-control study of Long Island women newly diagnosed with breast cancer during a 1-year period beginning in August 1996. A comparison group (controls) of women who did not have breast cancer was randomly selected from the two counties. Altogether, about 1,500 cases and 1,500 controls participated. This study was led by Marilie Gammon, Ph.D., University of North Carolina at Chapel Hill. Another study conducted with a subgroup of the study population who participated in Dr. Gammon's study investigated exposure to electromagnetic fields (EMFs) and breast cancer risk. This study was led by M. Cristina Leske, M.D., M.P.H., Stony Brook University.

In short, the reports arising from the LIBCSP did not identify any environmental factors that could be responsible for the high incidence of breast cancer on Long Island. Exceptions were a modest increase in risk of breast cancer from exposure to polycyclic aromatic hydrocarbons (PAH), a risk with proximity to an organochlorine-containing hazardous waste site, and a possible risk of breast cancer recurrence in women exposed to B-hexachlorocyclohexane. Dr. Gammon's study also confirmed many of the well-known breast cancer risk factors, including increasing age, having a family history of breast cancer, having a first child at a later age (age 28 or older in this study), never having given birth to a child, and having higher income.

Dr. Gammon's investigative team continues to analyze data collected in the initial case-control study of Long Island women. Other risk factors for breast cancer identified by the study include:

- Higher levels of aspirin intake are associated with a lower risk of hormone receptor-positive breast cancer.
- Higher consumption of fruits and vegetables has a protective effect on the risk of breast cancer.
- In a small case-control study, certain estrogen metabolites in urine were found to be associated with breast cancer risk.
- Weight gain since age 20 is associated with increased cancer risk.
- Increased risk in a subgroup of nonsmoking women living with spouse for over 27 years.

In addition, Dr. Gammon is conducting a followup study of women who were diagnosed with breast cancer and participated in her initial study. The goals of the study are to determine whether environmental factors examined in the initial study and other lifestyle factors influence disease-free survival and overall survival.

Dr. Leske's team continued to analyze data from the EMF study. Studying exposure to light and night, they report in June 2006 finding no association between overall shift work and breast cancer risk. Looking at evening and overnight shift work separately, women who were overnight shift workers were at lower risk for the cancer than women never working shifts. In addition, women who reported rising frequently during the week and turning on lights multiple times per night were found to be at increased risk for the cancer, a finding that has never been reported.

Environmental Exposure Studies in LIBCSP

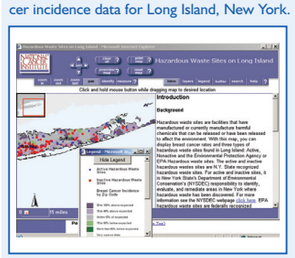
Principal Investigator (First author of published report)	Study	Environmental Exposures
Marilie Gammon, Ph.D., UNC at Chapel Hill (Gammon, 2002)	Breast Cancer and the Environment on Long Island Study	In blood serum: DDE; DDT; Chlordane; Dieldrin; 4 most frequently occurring PCB variants
Steven Stellman, Ph.D., Columbia University Stellman (2000)	Hospital-based case-control study on Long Island	In adipose tissue: DDE; Total pesticides; Total PCBs; Individual PCB variants
Steven Stellman, Ph.D. (Muscat, 2003)	Hospital-based case-control study	HCB; ß-HCH; OXC; TNC; DDE; DDT; DDD; Total pesticides; Total PCBs in breast adipose tissue; PCB variant #118; Self-reported termiticide exposure
Tongzhang Zheng, M.D., Sc.D., Yale University (Zheng, 1999)	Hospital-based case-control study in Connecticut	Hexachlorobenzene in breast adipose tissue
(Zheng, 1999)	Hospital-based case-control study in Connecticut	ß-benzene hexachloride in adipose tissue
(Zheng, 1999)	Hospital-based case-control study in Connecticut	DDE in breast adipose tissue; DDT in breast adipose tissue
(Zheng, 2000)	Hospital-based case-control study in Connecticut plus Tolland County case-control study	PCBs in blood serum; DDE in blood serum
(Zheng, 2000)	Hospital-based case-control study in Connecticut	PCBs in breast adipose tissue
(Zheng, 2000)	Hospital-based case-control study in Connecticut	Oxychlordane in breast adipose tissue; Trans-nonachlor in adipose tissue
Hazardous Waste Sites: Facilities that have manufactured or currently manufacture chemicals that can be released or have been released into the environment.		
Erin O'Leary, Ph.D., Stony Brook University O'Leary (2004)	NYS cohort, Long Island residents	Residence near hazardous waste site containing pesticides; Residence in a water district with any pesticides detected; Residence in area with prior agricultural land use
Polycyclic Aromatic Hydrocarbons (PAHs): Chemicals produced from combustion, cigarette smoke, burning of fossil fuels, and grilled and smoked foods.		
Gammon (2002)	Breast Cancer and the Environment on Long Island Study	PAHs as measured by PAH-adducts in blood
Electromagnetic Fields (EMFs): Invisible lines of force that surround any electrical device. Power lines, electrical wiring, and electrical equipment all produce EMFs.		
M. Cristina Leske, M.D., M.P.H., Stony Brook University (Schoenfeld, 2003)	Electromagnetic Fields and Breast Cancer on Long Island Study	EMF exposure based on: EMF meter reading; 24-hour EMFs in bedroom; 24-hour EMFs in most lived-in room; Ground current bedroom; Ground current most lived-in room; Wire coding: based on mapping of overhead wiring near home; a proxy for at-home magnetic field measurements
M. Cristina Leske, M.D., M.P.H. (Kabat, 2003)	Electromagnetic Fields and Breast Cancer on Long Island Study	Various electric blanket use patterns
M. Cristina Leske, M.D., M.P.H. (O'Leary, 2006)	Electromagnetic Fields and Breast Cancer on Long Island Study	Shift work and light at night

Abbreviations

ß-BHC = ß-benzene hexachloride
HCH = Hexachlorocyclohexane
TNC = *Trans*-nonachlor
PCB = Polychlorinated biphenyls
DDE = 1,1-dichloro-2,2-bis(4-chlorophenyl)ethylene
DDT = 1,1,1–trichloro-2,2-bis(4-chlorophenyl)ethane
DDD = 1,1-dichloro-2-(ortho-chlorophenyl)-2-(para chlorophenyl)ethane
EMF = Electromagnetic fields

Long Island Geographic Information System (LI GIS)

Geographic information systems (GIS) are powerful computer systems that can be used to store, manipulate, analyze, and display geographic locations simultaneously in order to investigate relationships between different data types, such as hazardous waste site location and breast cancer incidence. The LI GIS contains more than 80 datasets that include environmental, demographic, health, and breast cancer incidence data for Long Island, New York.



The LI GIS was developed and is maintained by NCI under a contract with L-3 Communications. Maps from the LI GIS data are being developed to provide the public a window into how the GIS works. Researchers can apply to use the LI GIS, as well as a suite of other GIS tools, or can download free custom statistical software extensions available for the LI GIS and for other GIS applications via the Web site: *www.healthgis-li.com.*

Breast Cancer and the Environment Research Centers (BCERCs)

A new generation of research is now underway. Funded in 2003, the Breast Cancer and the Environment Research Centers (BCERCs) take a fresh approach to the study of environmental causes of breast cancer by focusing on young girls, rather than on adult women, which overwhelmingly has been the approach in the past. Early puberty has been shown to be a risk factor for breast cancer, and perhaps the developing breast is more vulnerable to environmental exposures. This 7-year project is funded by NIEHS in collaboration with NCI. (NCI contributes 40 percent of the funding.)

Four BCERCs are studying the impact of prepubertal exposures that may affect pubertal development and predispose a woman to breast cancer. The BCERCs were developed and organized into two projects, epidemiology and animal research, and Community Outreach and Translation Cores (COTCs), which include representatives from the advocacy community, as a means of ensuring integration of epidemiology research into meaningful animal research studies, incorporation of animal research efforts into epidemiologic settings, communication of animal and epidemiology research results to the public, and collaborations between advocates and scientists throughout the BCERC research agenda.

Using animals, the BCERCs are studying the development of mammary tissue and the effects of specific environmental and hormonal agents. Using principles of epidemiology, they are enrolling different ethnic groups of young girls and studying their life exposures to a wide variety of environmental, nutritional, hormonal, and social factors that impact puberty.

The BCERCs function as a consortium of basic scientists, epidemiologists, research translational units, and community advocates within and across centers. The centers and principal investigators are:


Sue Heffelfinger, M.D., Ph. D.
University of Cincinnati


Jose Russo, M.D.
Fox Chase Cancer Center


Robert Hiatt, M.D., Ph.D.
University of California at San Francisco


Sandra Haslam, Ph.D.
Michigan State University

Driving Breast Cancer Research: The Role of Advocates

Thanks to the dedication of breast cancer advocates, it is now commonplace to have advocates serve in many different capacities in the research process (Collyar D, 2005). Advocates interacting with the research community on breast cancer research projects is the norm.

Diane Sackett Nannery, pictured with poster of first U.S. Postal Service breast cancer awareness stamp. A Long Island postal worker and breast cancer survivor, she was instrumental in issuance of this first-ever breast cancer awareness stamp. Mrs. Nannery died of the cancer in 2003.

At the time the LIBCSP began, the development of roles for advocates, or consumers, in the breast cancer research process was largely uncharted. Advocates had many roles in the LIBCSP that were extraordinary for the times. They had representation on a National Institutes of Health (NIH) Study Section (peer-review group responsible for grant application review), the *ad hoc* advisory group for the LIBCSP, and the oversight committee for the LI GIS. They served as advisors on individual studies and established community liaisons for each study. Meetings periodically were held on Long Island to bring together the advocates and researchers. It was a beginning.

Today—a decade later—consumers are part of the fabric of BCERCs. In particular, the advocates in the COTCs help drive research objectives and initiatives, translate research findings, and often interact with breast cancer researchers. Advocates also serve on the overall working group for the BCERCs.

Readers may be interested in a *Nature Reviews Cancer* article by Dr. Deborah Winn that provides more information about the LIBCSP and other research conducted on breast cancer and the environment. (Nat Rev Cancer 2005 Dec;5(12):986-94)