Puberty, Breast Cancer, and the Environment

A REPORT FROM THE

Bay Area Breast Cancer
and the Environment
Research Center

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Executive Summary

What can studying puberty reveal about how breast cancer develops and how it can be prevented? This is the question that drives our work at the Bay Area Breast Cancer and the Environment Research Center (BABCERC).

Breast cancer is a disease caused by both genetic and environmental factors. Over the past decade, it has become increasingly clear that exposure to estrogens and estrogen-like compounds found in chemicals in our environment can increase a woman's risk of developing breast cancer.

Our research is exploring the hypothesis that puberty is a *window of susceptibility* in which the breast cells might be especially vulnerable to these potential carcinogens, which may in turn affect the risk of breast cancer in later life.

We believe that by broadening the focus of research on breast cancer and the environment to include children and adolescents, we have the potential to gain new insights into what causes breast cancer to occur and how early exposures to carcinogens may affect breast tissue in ways that increase breast cancer risk in adulthood.

The BABCERC is one of four research centers that were awarded funding, in 2003, from the National Institute of Environmental Health Sciences and the National Cancer Institute to conduct research on breast cancer and the environment.

Our center comprises three projects:

1. **The Basic Science project**, in which we conduct research on mice and human tissue to investigate how the mammary gland develops and how that development is affected by environmental exposures.
2. **The Epidemiology project**, which is following a group of young girls for five years as they go through puberty to investigate how genes, the environment, biology, lifestyle, socio-economic factors, and body composition, separately and together, influence the age that puberty begins. It is one of the most comprehensive studies of environmental influences on puberty ever conducted.
3. **The Community Outreach project**, whose staff works with the Basic Science and Epidemiology projects to integrate the community's interests and concerns into the research agenda, develop public health messages, and disseminate and explain research findings.

Our transdisciplinary, community-based approach has enabled us to contribute in important ways to the breast cancer field. Our findings have been published in numerous journals, presented at breast cancer conferences, and discussed at town hall meetings. We also have developed educational materials for the community on a wide range of breast-cancer-related topics.

We hope our research will result in public health policies that help decrease the exposure of girls and women to the environmental chemicals that are found to increase breast cancer risk, and in the establishment of public health programs that teach women about lifestyle choices that can reduce their risk of developing the disease.

We are proud to serve as a model for community involvement in cancer research and to be leaders in the effort to focus research attention and public health policies on breast cancer and the environment.

Introduction

What can studying puberty reveal about how breast cancer develops and how it can be prevented? This is the question that drives our work at the Bay Area Breast Cancer and the Environment Research Center (BABCERC).

Myriad factors, including biology, the environment, lifestyle, and body composition, influence the age at which puberty begins. Studies have shown that women who start menstruating at an early age have an increased risk of developing breast cancer. Our research stems from the hypothesis that early environmental exposures can influence mammary gland or breast development and the age when puberty begins, which may in turn affect the risk of breast cancer in later life.

Over the past decade, it has become increasingly clear that exposure to estrogens and estrogen-like compounds can increase a woman's risk of developing breast cancer. This estrogen exposure can come from the estrogen that a woman's body makes naturally, from the hormone therapies used to treat menopausal symptoms, or from the estrogen-like compounds found in products such as children's toys, personal care products, plastic drinking bottles, and pesticides. At the BABCERC, we are exploring whether it matters if and when these exposures take place and, if so, what types of interventions can prevent breast cancer from occurring.

For the breast to grow and develop normally during puberty, breast cells must divide rapidly. However, each time a cell divides, a genetic "mistake" can occur. These mistakes can happen naturally, or they can result from a cell's exposure to certain environmental factors. This makes puberty a *window of susceptibility,* in which the breast cells might be especially vulnerable to potential carcinogens.

The best evidence to support our hypothesis that puberty is a *window of susceptibility* to

What Does "the Environment" Mean?

If you are like most people, you probably think of "the environment" as the air, water, and land that surrounds you. And, of course, you would be right. But when it comes to epidemiology, the branch of medical science that investigates the cause of disease, "the environment" is all that and more. In epidemiology, environmental factors are any of the exposures that might increase or decrease a person's risk of getting a disease, factors that are not part of that person's biology.

BABCERC investigators think of "the environment" in this broader sense. Our studies are looking at the role of environmental chemicals, in particular at female hormone or estrogen-like compounds found in personal care and household products. We are also looking at diet and exercise; stress and other psychological factors; and neighborhood proximity to grocery stores that stock fresh fruits and vegetables and to parks or gyms that offer opportunities for physical exercise.

environmental factors comes from epidemiological studies that have looked at the relationship between radiation exposure and breast cancer. Some of these studies show that women who are under the age of 20 when exposed to ionizing radiation from x-rays or cancer treatments have a higher risk of developing breast cancer than do women who are exposed at an older age. Others have shown that girls who were exposed to radiation from the atomic bombings of Hiroshima and Nagasaki during World War II were much more likely to develop breast cancer if they were in the age range when puberty occurs than were similarly exposed older girls or adult women.

More recently, epidemiologists have looked at whether the estrogen-like compounds that are believed to increase breast cancer risk may also affect puberty and breast development. These studies have shown that:

- Girls who were exposed pre-natally *(in utero)* to high levels of PCBs (chemicals that have been found in fish, high-fat foods, and water) and DDT (a pesticide) develop pubic hair earlier than girls who had a lower exposure, although they do not start their periods at a younger age.
- Girls who had premature breast development had higher levels of phthalates (a chemical found in plastics, personal care products, and fragrances).
- Girls who were exposed to a high level of lead started puberty and menstruation later.

Findings from our studies will contribute to the larger body of research that is investigating which environmental factors contribute to early puberty and which exposures that occur in puberty may increase breast cancer risk later in life.

Exploring Windows of Susceptibility

The female breast changes many times over the course of a lifetime. Although these changes may seem to occur gradually, there are specific time periods when more rapid changes take place. Some of these changes occur:

- Before birth *(in utero),* when breast cells begin to form during fetal development.
- During puberty, when the breast develops; this is when the ducts, which carry fluid through the breast, and the lobes, where milk is produced, begin to grow.
- During pregnancy; this is when the breast becomes fully mature, as it prepares to make milk.
- During lactation, as milk flows from the lobes and through the milk ducts.
- During menopause, as the breast will no longer need to make milk.

Scientists have proposed that the physiological changes that occur during these distinct time periods may make breast cells more vulnerable. At the BABCERC, we refer to these time periods when the breast may be more at risk as *windows of susceptibility.* BABCERC biologists are studying the windows that occur throughout the life span in animal models and cell systems, beginning before birth, when the breast is first forming. Our epidemiologists are studying the window that occurs during puberty in girls, when the breast is developing.

Environmental Chemicals Studied, Major Sources of Exposure, and Reasons We Are Studying Them

WHAT	WHERE	WHY STUDY THEM
Phthalates	Plastics, personal care products, fragrances	Known hormonal agents, they have received extensive media attention and are of great concern to the community.
Polychlorinated biphenyl (PCB) congeners	Contaminated food (fish, high-fat foods) and water	Known to have estrogenic activity, they have received extensive media coverage and are of great concern to the community.
Phenols (e.g., bisphenol A)	Drinking bottles, food can liners, water pipes, dental sealants	Known to have estrogenic activity, phenols have received extensive media attention and are of great concern to the community.
Perfluorinated compounds (PFCs)	Contaminated air and water, industrial sources	Experimental animal research suggests they affect pubertal development.
Phytoestrogens (e.g., isoflavones and lignans)	Soy products and other foods in the diet	Women with breast cancer have many questions about eating soy; studies suggest that girls in Japan whose diets contain high levels of soy are less likely to develop breast cancer as adults.
Cotinine	Tobacco smoke exposure	Tobacco smoke is a known carcinogen and has hormonal activity.
Polybrominated diphenyl ethers (PBDEs)	Brominated flame retardants, furniture foam, mattresses, carpet padding, hard plastic used in electronics, contaminated air, water, and food	Animal studies suggest PBDEs may disrupt thyroid and reproductive functions.
Organochlorine pesticides	Contaminated food and water; persistent in the environment, now in diet and breast milk	Known estrogenics, they are a focus of breast cancer advocates.

Advocacy in Action

Breast cancer and environmental justice advocates played a critical role in pushing government agencies to focus attention and resources on the environmental causes of breast cancer. These advocates didn't introduce the idea that environmental toxins might increase the risk of cancer. Scientists had been discussing that possibility since the early 1900s. Nor did these advocates lack research to support their concerns. Studies had shown that scientists could induce cancer by injecting certain chemicals into mice or rats. The problem was that scientists didn't have the tools necessary to accurately measure environmental exposures in humans, which meant few investigators were drawn to this area of research. That's what these advocates set out to change, and they worked tirelessly to draw public attention to the need for scientists to conduct more and better studies on the potential environmental causes of breast cancer in order to prevent the disease from occurring.

The need to learn more about environmental exposures resulted in scientific advances that made it easier to measure low levels of chemicals in human tissue. This field, called *biomonitoring*, has provided new ways for breast cancer researchers to investigate the concerns that breast cancer advocates have raised about the relationship between environmental exposures and breast cancer risk and has helped push breast cancer prevention research forward.

What Can We Look For?

SOME EXAMPLES OF WHAT CAN BE MEASURED OR STUDIED IN BODILY FLUIDS
Blood—cadmium, hormones, lead, mercury, organochlorine pesticides, PBDEs, PCBs, PFCs
Breast milk—cotinine, dioxins, furans, organochlorine pesticides, PCBs
Saliva—DNA, hormones
Urine—metals, pesticides, phthalate metabolites, phytoestrogens, repellants

What Is Biomonitoring?

Biomonitoring is used to measure people's exposure to potentially harmful natural and manufactured chemicals in the environment. Researchers monitor and compare over time the levels of certain chemicals or other substances in human blood, urine, breast milk, saliva, and fatty tissue. These chemicals and substances can get into the body through the air we breathe, the water we drink, and the food we eat. Biomonitoring can:

- Assist in determining the links between environmental exposures and pollution-related diseases.
- Provide, in combination with environmental monitoring, detailed information about differences in exposures across geography, race, ethnicity, and socio-economic status.
- Illuminate the relationships between genetic predispositions or sensitivities and disease outcomes.
- Be used in epidemiological or clinical studies to explain the rates of diseases in relation to environmental causation once associations are known.

Although the ability to measure the presence of chemicals in the body has improved, researchers are only beginning to understand the health implications of these findings and whether they are indicators of health risk.

Why Study the Environment?

Cancer is a disease that is caused by both genetic and environmental factors. Some women are born with a genetic mutation that dramatically increases their risk of developing breast cancer. But for all women, including women with a genetic mutation, environmental factors such as diet, exercise, and chemical exposures affect genes in ways that determine whether cancer actually develops.

Women can't change their genes. But public health policies can help decrease their exposure to the environmental chemicals that are found to increase breast cancer risk, and public health programs can teach women about lifestyle choices that can reduce their risk of developing the disease.

Over the past two decades, scientific advances, public policy developments, and breast cancer and environmental health advocates have each contributed in unique ways to advance the understanding of how genes and the environment interact to increase breast cancer risk. Some of the events that have made this possible include:

- The birth of a field called molecular epidemiology, which uses the latest scientific techniques to identify changes in genes and molecules that are associated with an increased cancer risk following exposure to known cancer-causing agents.
- Published reports on suspected environmental risk factors for breast cancer, such as pesticides (DDT/DDE and PCBs), electromagnetic fields, and byproducts of charbroiled foods.
- The establishment of the National Breast Cancer Coalition, which created a strong community and lobbying presence that links breast cancer advocacy organizations into a powerful national voice.
- The development of the Breast Cancer Research Programs in the Department of Defense and the State of California, which have involved the advocacy community at all levels.
- The founding of the Silent Spring Institute, which developed a team to lead the Cape Cod Breast Cancer and the Environment Study and the Newton Breast Cancer Study, which were both funded by the Massachusetts Department of Public Health.
- The Long Island Breast Cancer Study, which investigated whether environmental factors were responsible for the increased breast cancer rate seen in Suffolk and Nassau counties on Long Island, New York.
- The attention drawn by the National Institute of Environmental Health Sciences to the need for community-based participatory research.
- The Centers for Disease Control and Prevention's initiation of the National Health and Nutrition Examination Survey (NHANES), which collects health data from people throughout the U.S. to monitor the nation's health, determine risk factors for diseases, develop public health policies, and design health programs. NHANES introduced biomonitoring to its program in 2001, and it is collecting information on exposures to 250 chemicals.
- Advocacy efforts that led to the passage, in 2008, of the Breast Cancer and Environmental Research Act, which resulted in the establishment of an Interagency Breast Cancer Coordinating Committee to enhance efforts to study potential connections between breast cancer incidence and environmental factors.

These developments laid the groundwork for, and helped shape many aspects of, the breast cancer research taking place today.

BREAST CANCER STATISTICS

Aside from non-melanoma skin cancer, breast cancer is the most common form of cancer in women. Nationwide, it is the number one cause of cancer death in Hispanic women, and the second most common cause of cancer death in white, black, Asian/Pacific Islander, and American Indian/Alaska Native women.

In 2005 (the most recent year for which statistics are available), 186,467 women and 1,764 men were diagnosed with breast cancer, and 41,116 women and 375 men died from the disease.

Quick Facts About Breast Cancer in California

- In 2009, it is estimated that 22,115 women will be diagnosed with breast cancer and that 4,170 will die from the disease.
- 55 percent of California women who get breast cancer are under age 65.
- The San Francisco Bay Area has one of the highest breast cancer rates in California.
- White women are more likely to get breast cancer, but African-American women are more likely to die from breast cancer after a diagnosis.
- Between 1998 and 2005, the female breast cancer incidence rate in California decreased by 8 percent, and the mortality rate decreased by 29 percent.
- The breast cancer rate for Asian women in California is going up, while the rates for other California ethnic groups are dropping.

What Is Your Risk of Getting Breast Cancer?

You've probably seen this statistic: One in eight women will get breast cancer. But what does it really mean? The "one in eight" statistic is your likelihood at birth of being diagnosed with invasive breast cancer at some point during your lifetime. And because your risk for breast cancer increases as you age (remember, it typically takes decades for a normal cell to turn into a cancer cell), your risk of being diagnosed with breast cancer differs at different points in your life.

- From age 30 through age 39, it's 1 in 233
- From age 40 through age 49, it's 1 in 69
- From age 50 through age 59, it's 1 in 38
- From age 60 through age 69, it's 1 in 27

Source: National Cancer Institute, "Probability of Breast Cancer in American Women," http://www.cancer.gov/cancertopics/factsheet/detection/probability-breast-cancer.

SOURCES:

California Department of Public Health, "Quick Facts About Breast Cancer in California," http://www.cdph.ca.gov/HealthInfo/Pages/QuickFacts.aspx.

California Breast Cancer Research Program, "Breast Cancer Cases and Deaths in California," http://www.cbcrp.org/publications/papers/BCinCA/page_03.php.

American Cancer Society, California Division, and Public Health Institute, California Cancer Registry, *California Cancer Facts and Figures 2009,* Oakland, CA, September 2008, http://www.nccc.org/atf/cf/{C580CD0D-E445-46F8-97CF-443A3570F63F}/ACS2009.pdf.

Significant Events That Advanced Research on Breast Cancer and the Environment

1991	National Breast Cancer Coalition forms.
1992	Department of Defense initiates the Breast Cancer Research Program.
1993	Congress mandates the Long Island Breast Cancer Study Project.
1993	Members of the Massachusetts Breast Cancer Coalition establish the Silent Spring Institute.
1997	The California Breast Cancer Research Program funds the Adolescent Risk Factors Study in Marin County.
2001	The National Institute of Environmental Health Sciences and the National Breast Cancer Coalition co-host a "Brainstorming Workshop on Breast Cancer and the Environment."
2002	International Summit on Breast Cancer and the Environment Research held in Santa Cruz, California, and funded by the CDC.
2002	At a town meeting in Marin County, California, sponsored by Zero Breast Cancer, NIEHS announces that it will establish Breast Cancer and the Environment Research Centers.
2003	Bay Area Breast Cancer and the Environment Research Center is selected as one of four BCERCs.

Source: Breast Cancer and the Environment Research Centers, Progress Report. (Unpublished preliminary results. A document prepared for presentation to the National Cancer Institute, Board of Scientific Advisors) March 2009.

A Collaborative Effort

Bay Area breast cancer advocates have been at the forefront of the effort to draw attention to potential environmental causes of breast cancer. Their motivation: statistics that show that the Bay Area has one of the highest breast cancer rates in the world. Breast cancer advocates were not the only ones concerned that no one could explain these high breast cancer rates. Scientists and public health officials also recognized that the high cancer rates pointed to a need for funds to be directed to research studies that could advance the understanding of how environmental factors increase breast cancer risk.

These efforts were solidified by the California Breast Cancer Research Program (CBCRP), which was established by the state legislature in 1993 to fund breast cancer research throughout California. The CBCRP's emphasis on community-based participatory research, which encourages collaboration between researchers and community members, helped to form and strengthen relationships between scientists and advocates throughout California.

These developments and partnerships set the stage for Bay Area scientists and breast cancer advocates to collaborate on a grant that was submitted in 2002 to the National Institute of Environmental Health Sciences and the National Cancer Institute. In October 2003, the Bay Area learned that it was one of four Breast Cancer and the Environment Research Centers (BCERCs) that had been selected to be part of this new initiative. The three other institutions that received these competitive awards, which totaled $35 million over a seven-year period, were the University of Cincinnati, Fox Chase Cancer Center in Philadelphia, and Michigan State University in East Lansing.

The four BCERCs operate independently but work collaboratively. We at the BABCERC meet regularly with the members of the other centers to

discuss our research and our findings. This allows us to build on one another's work, determine when it would be appropriate to pool our data to investigate a specific area of interest, share information about community outreach programs and materials, and engage in the conversations that will help us push this field of research forward.

Meet the BABCERC

The Bay Area Breast Cancer and the Environment Research Center comprises three projects:

1. **The Basic Science project**, which is studying how the normal mammary gland (the breast) develops and how it responds to environmental exposures. Our laboratory scientists are conducting research on mice and human tissue.

2. **The Epidemiology project**, which is following a group of young girls for five years as they go through puberty. Our researchers are trying to identify the environmental factors that influence the age at which a girl starts puberty. This study is called the CYGNET Study (Cohort study of Young Girls' Nutrition, Environment, and Transitions).

3. **The Community Outreach project**, which works with the Basic Science and Epidemiology projects to integrate the community's interests and concerns into the research agenda. This project, formally known as the Community Outreach and Transition Core, hosts programs that bring together breast cancer advocates, scientists, physicians, and the community to discuss our scientific findings, and it develops public health messages based on our findings.

Our work is structured around two core beliefs:

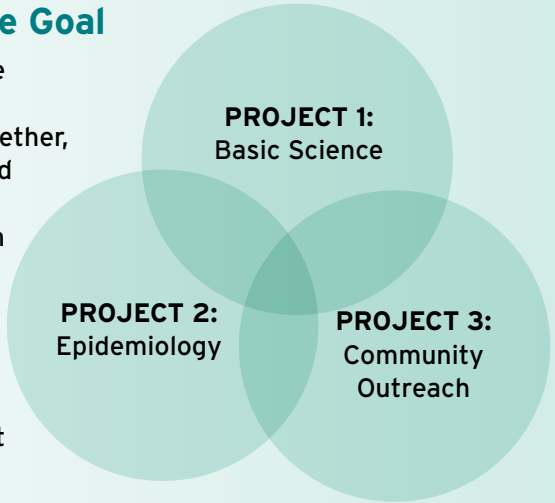
1. That a transdisciplinary approach that brings together experts who have been trained in an array of scientific techniques and methodologies is the optimum way to learn more about the relationships between the environment and breast cancer risk.

2. That a community-based participatory research approach can improve public health when scientists work with the community as equal partners in the design and conception of medical research, respond to a community's interests and concerns, and educate the community about scientific findings.

The structure of our BABCERC fosters the crosstalk between and among scientists and the community that is necessary to advance the research into what causes early puberty and breast cancer. Our framework allows us to pursue the conversations and studies that are possible only when researchers share information across disciplines and areas of expertise. For example, our basic scientists, who are investigating how chemicals and genetics drive

Three Projects: One Goal

Each project brings unique strengths and skills to the BABCERC. By working together, we are able to combine and learn from study findings, share information that can inform and advance another project's work, and translate breast cancer and environmental research into policies and programs that can prevent breast cancer.



What Is Transdisciplinary Science?

Interest in transdisciplinary science has grown dramatically over the past 25 years. The term is used to describe research that attempts to look at a topic from a new perspective or with a new approach by integrating concepts and methods from multiple research fields. Transdisciplinary science breaks down the barriers between disciplines in traditional research, where experts focus solely on their own field, and fosters conversations across disciplines such as biology, psychology, epidemiology, and oncology. Such conversations can lead to new ways of thinking about and studying a particular problem, such as what causes breast cancer.

breast development in mouse models, are able to discuss their findings with our epidemiologists and work with them to determine how this research can be further pursued by studying the urine, blood, or saliva samples obtained from the girls in the epidemiologic study. In turn, our epidemiologists are able to discuss their interests and findings with our basic scientists, who can use their mouse models to assess the potentially harmful effects of specific environmental exposures. In addition, both groups of researchers are able to get feedback from our Community Outreach project about the research questions they are pursuing and the extent to which they respond to the community's concerns.

The BABCERC is headed by Dr. Robert Hiatt, Director of Population Science and Deputy Director of the University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center. The Basic Science project is led by Dr. Zena Werb, Professor of Anatomy at the University of California, San Francisco; the Epidemiology project is led by Dr. Lawrence Kushi, Associate Director of the Division of Research at Kaiser Permanente Northern California; and the Community Outreach project is led by Janice Barlow, the Executive Director of Zero Breast Cancer.

The BABCERC includes breast cancer experts and collaborators at:

- California Department of Public Health
- Kaiser Permanente of Northern California
- Lawrence Berkeley National Laboratory
- Marin County Department of Health and Human Services
- Roswell Park Cancer Institute, New York
- San Francisco Department of Public Health
- University of California, Berkeley
- University of California, San Francisco
- University of Michigan
- Zero Breast Cancer

These individuals work alongside a team of community partners, including those from:

- Alameda County Department of Public Health
- Bay Area Breast Cancer SPORE Advocacy Group
- Bayview Hunters Point Health and Environmental Assessment Task Force

Our work has resulted in numerous presentations, publications, and papers that have increased an awareness about how environmental factors can influence breast cancer risk. We believe that by discovering possible environmental causes of breast cancer, we will be able to better protect future generations from developing this disease.

MEET DR. ROBERT HIATT

Q: Why were you interested in leading the BABCERC?

A: Breast cancer is my main research interest, and I have had a long-standing relationship with local breast cancer advocates. When I worked at the National Cancer Institute, I was responsible for overseeing studies taking place throughout the country that were looking at high breast cancer incidence in specific localities, and I became familiar with the challenges in implementing large-scale cross-disciplinary studies. When it was announced that grants were being made available to start Breast Cancer and the Environment Research Centers, I was eager to win one for the Bay Area.

Q: As a scientist, what do you want the community to understand about this project?

A: This project is very unusual in that it was initiated by breast cancer advocates but began after a period of thoughtful discussion between scientists and advocates about the best way to advance knowledge about the causes of breast cancer and how to prevent it. Scientist-advocacy interaction was built into the BABCERC from its inception, and it has continued successfully throughout the project.

Q: What is the most gratifying aspect of this work?

A: Honestly, it has been difficult to "herd cats" in this large and complicated research project, but I am most gratified to see the people involved in this project learning things from each other that would normally be out of their field of vision. This has been true for the laboratory scientists, population scientists, advocates, and community members.

Q: What do you see as the BABCERC's most significant research finding?

A: We have found that girls are going through puberty even earlier than previously reported and that the age they begin puberty varies markedly by their racial and ethnic background and their socio-economic status. And when we combined our data with the other two BCERCs studying this issue, it appears that the age that puberty begins may also vary based on where the girls live in the U.S. We have also learned some fascinating things about normal breast development and what changes lead to cancer in the mice we are studying. We are still analyzing data on environmental toxins that might influence how puberty develops, so the most important research findings are probably still yet to come.

Robert Hiatt, MD, PhD, heads the BABCERC. He is the Director of Population Science and Deputy Director of the University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center.

CHAPTER 1

Basic Science, Breast Cancer, and the Environment

What causes a normal breast cell to turn into a cancer cell? Despite decades of breast cancer research, this mystery has yet to be solved.

We know that cancer cells are normal cells gone astray, and that it is damage to the cell's genetic structure that causes it to take on this bad behavior. We also know that a normal cell doesn't just turn into a cancer cell overnight. It typically takes decades for a series of genetic mistakes to transform a cell into a full-fledged cancer cell that has the capacity to grow uncontrollably, invade nearby areas, and spread to other parts of the body. It is now also becoming clear that to fully understand how cancer develops, we must learn more about the ways in which the tissues that surround the cancer cells help foster a tumor's growth.

To advance the understanding of what causes breast cancer to occur, the BABCERC's Basic Science project is studying how the mammary gland develops and how that development is affected by environmental exposures. We have conducted our research at the University of California, San Francisco and at Lawrence Berkeley National Laboratory in laboratory animals (mice) and in animal and human cells. Cancer scientists refer to these as "animal models" and "cell culture models," respectively. We aim to:

- Identify and describe the molecular and structural changes that occur in the mammary gland over its life span. (In mice, the term "mammary gland" is used to refer to the tissue that in women develops into the breast.)
- Determine how exposures to potential carcinogens during a window of susceptibility, such as puberty, influence future breast cancer risk.

Basic Science: Molecules and Cells in Action

Basic science is the research field that investigates how or why a certain process occurs. Basic science encompasses fields such as molecular and cellular biology, genetics, and physiology. It provides a framework for thinking about how the breast develops and what triggers the changes that make it possible for a normal cell to turn into a cancer cell. The information gleaned from basic science research is later translated, or applied, to research aimed at developing new methods of patient care and disease prevention.

Basic science cancer research is conducted in two ways:

- *in vivo*—studies are done in cells in a living organism
- *in vitro*—studies are done in a laboratory dish or test tube

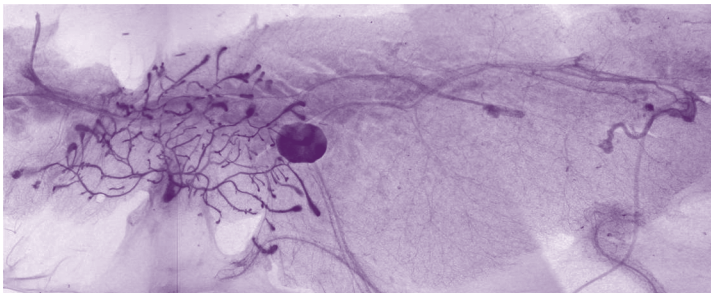
Our Focus on Puberty

When puberty begins, cells that have been sitting quietly in the female mammary gland receive hormonal messages that tell them it is now time to get to work. In response, these cells begin to grow and divide rapidly. Their mission: to form the ductal tree that characterizes an adult breast. When a pregnancy occurs, the breast ducts will go through another transformation. Only then will they be fully formed and able to make and then transport milk from the ductal lobes to the nipple.

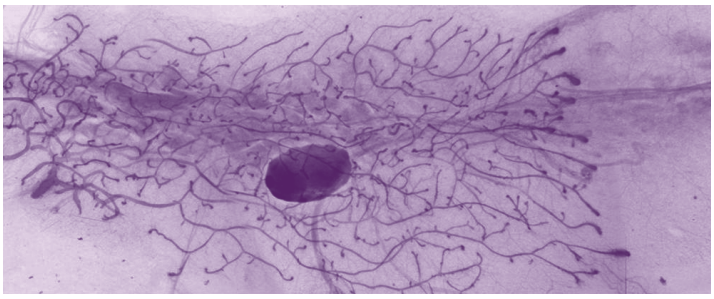
At the BABCERC, we are using technologies that can analyze genes, proteins, and metabolites to learn what effect chemicals or other environmental exposures have on the mammary gland at specific points in the life span. To model how cancer occurs, we expose mice and human breast cells to low-dose ionizing radiation at different stages of development: pre-puberty, puberty, pregnancy, and old age. We chose ionizing radiation—the type of radiation in an x-ray—because it is a known carcinogen and because exposure to ionizing radiation during puberty has been shown to increase breast cancer risk later in life. Studying how a known carcinogen affects breast cells will also help us identify the best methods for evaluating whether other environmental factors may also increase breast cancer risk.

Our transdisciplinary approach allows us to bridge the gap between animal and cell models and humans.

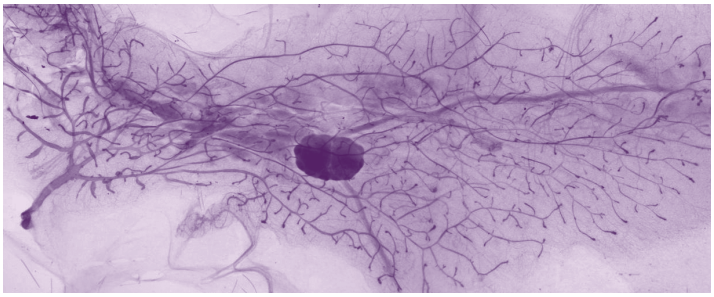
A Mouse Mammary Gland During Puberty



Five-week-old mouse, near the beginning of puberty. The ducts extend from the nipple to the lymph node (the dark oval structure). The bulbous structures at the end of the primary ducts are the terminal end buds, where cell proliferation and ductal invasion into the fat pad takes place.



Seven-week-old mouse, well into puberty. The ducts extend well past the lymph node.



Ten-week-old mouse, at the end of puberty. Cell proliferation and ductal invasion have stopped. The entire mammary pad is now filled with mammary ducts, and the terminal end buds are no longer present.

OF MICE AND WOMEN

Why do scientists use mice to study how breast cancer occurs in women?

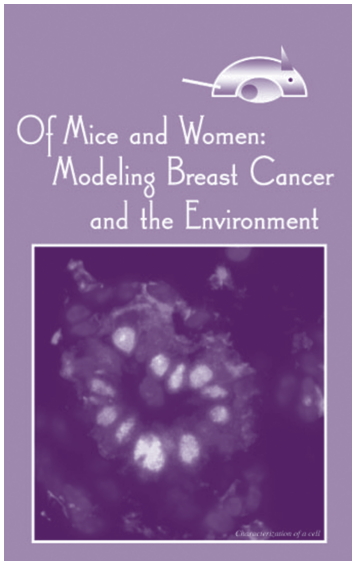
That is just one of the questions Mary Helen Barcellos-Hoff, PhD, answers in *Of Mice and Women: Modeling Breast Cancer and the Environment,* a DVD developed by the Basic Science and Community Outreach projects.

The Community Outreach project recognized that the trans-disciplinary nature of the BABCERC's research created the perfect setting for developing a DVD that could help breast cancer advocates and community members understand basic science. Dr. Barcellos-Hoff, who recently moved from the Lawrence Berkeley National Laboratory to New York University, was eager to be part of the project, and she worked hand in hand with Community Outreach project members to develop the DVD and its accompanying scientific glossary, which explains in easy-to-understand terms how basic scientists pursue research questions and the advantages and disadvantages of using mice models to study breast cancer in humans.

The DVD explains, for example:

- The similarities between mouse mammary glands and women's breasts.
- How scientists create a genetically engineered mouse and why their research into the causes of cancer can be done faster using this type of mouse than it ever could be done in humans.
- How scientists use mice to identify molecular markers that can be used to assess a woman's breast cancer risk or identify targets for new methods of chemoprevention.
- Why the next time you read about an advance in breast cancer research you may want to thank a mouse!

Want to learn more? The DVD *Of Mice and Women* can be purchased on our Web site, http://bayarea.bcerc.org.



The *Of Mice and Women* education kit is an innovative tool that breast cancer advocates and community members can use to facilitate a greater understanding as to why mice are used in breast cancer research. The kit includes a 35-minute DVD and a glossary of scientific terms related to breast cancer.

MEET DR. PAUL YASWEN

Q: Why were you interested in being part of the BABCERC?

A: I subscribe to the idea that cross-fertilization of ideas by people with widely divergent backgrounds and expertise can lead to creative insights that might not otherwise be realized. I also recognize the responsibility, and enjoy the challenge, of trying to communicate the significance and rationale of my own scientific endeavors to the greater community.

Q: What do you want the community to understand about basic science?

A: I want the community to understand the difficulties, but also the necessity, of using scientific methodology to bear upon the breast cancer problem. Acquiring useful knowledge is a hard-fought enterprise, and there are always caveats associated with knowledge gained by correlative observations and controlled experiments. Nevertheless, such knowledge is essential for rational decision making and establishing public policies.

Q: Why is it so hard to identify the environmental factors that increase breast cancer risk?

A: Unlike infectious diseases or acute toxicities that have single root causes, the causes of breast cancer are likely to be multifactorial and diverse. The contributions of each single factor are likely to be small and to depend on many other factors present. Also, the factors probably interact with each other over the decades-long process that precedes the development of a breast tumor in ways that we can currently only guess at. While we have ideas about the players and processes involved, our understanding of how breast cancer develops is still fuzzy at best.

Q: What's been your most interesting BABCERC research finding?

A: We have found that ionizing radiation, which is perhaps the most studied and best-understood breast carcinogen, not only causes genetic mutations but may also promote the development of breast cancer in other ways. We've begun to realize that breast cancers are not simply lumps of homogeneous cells; they are caricatures of normal tissue development. By affecting how cells communicate and interact, environmental factors like radiation are able to promote the growth of cells that have the potential to go on to become cancerous.

Paul Yaswen, PhD, is a co-investigator on the Basic Science project. He is a staff scientist in the Life Sciences Division of the Lawrence Berkeley National Laboratory.

Testing Hypotheses

Our Basic Science project conducted *in vivo* studies in mice to test hypotheses about the genetic and cellular mechanisms involved in both normal mammary gland development and the initiation of breast cancer. Using mice allows us to conduct experiments that could never be performed on human subjects.

Because mice are widely used in breast cancer research, it would be easy to assume that these animals naturally develop cancer of the mammary gland. But that's not the case. To conduct our studies, we must use mice that have been genetically altered to develop breast cancer. We couldn't move breast cancer research forward without such animal studies. But we also know that what happens in mice does not always happen in humans. That's one reason we have also conducted *in vitro* studies with human cells and tissue to investigate and confirm some of the observations we made in our in vivo animal research. But there are limitations to this approach as well.

That's why our transdisciplinary approach is so important: It allows us to bridge the gap between animal and cell models and humans. Our Epidemiology project has repeatedly used the Basic Science project's findings to develop its own hypotheses. It also has used the Basic Science project's findings to determine which genetic changes and biologic markers it should test for in its studies. In turn, the Basic Science project has used the Epidemiology project's findings to develop new hypotheses about environmental exposures that occur during puberty—hypotheses that can be tested in cell and animal models.

Our Research Questions

The Basic Science project is exploring questions such as:

- How do the hormones made by the female body regulate mammary gland development?
- Which molecules and proteins play a role in mammary gland development?
- Which genes control the normal cell cycle in the breast?
- Which genes control the branching process that results in the ductal tree that grows during puberty?
- How does the tissue that surrounds the breast tumor support or influence the tumor's growth?
- How does radiation exposure damage the breast tissue and increase breast cancer risk or aid tumor growth?
- How does radiation cause the growth of new blood vessels?

Puberty: Embarking on the Ability to Reproduce

What Is Puberty?

Puberty is the time in a young girl's life when a series of hormonal, physiological, cognitive, and socio-emotional changes occur. These changes get under way when an area of the brain called the hypothalamus sends chemical messages to the ovaries that trigger the hormonal and physical processes that tell the body it is now time to develop the ability to reproduce.

When Does Puberty Begin?

Puberty actually begins while a girl is still a fetus in her mother's womb. That's when a girl develops the luteinizing hormone-releasing hormone (LHRH) pulse generator in the hypothalamus. The generator, which the body turns off shortly after birth, gradually reawakens when the hypothalamus starts to release a hormone called gonadotropin. This gradual reawakening, which is usually impossible to detect, varies in age from person to person and precedes the first signs of visible physical changes by a year or two.

When Do the Physical Changes Associated With Puberty Become Visible?

The physical changes that accompany puberty include the appearance of breast "buds" (called *thelarche*) and pubic hair (called *pubarche*). This normally begins between the ages of 8 and 13. A girl's first menstrual period (called *menarche*) typically occurs about two years after thelarche. In the U.S., 12 is the average age of menarche.

Early Puberty: What Are the Risk Factors?

Early puberty can expose a woman to greater amounts of estrogen over her lifetime. Genetic, nutritional, environmental, and psycho-social risk factors have been identified for early puberty. These include:

- Genetic and racial/ethnic heritage. In the U.S., African-American girls tend to enter puberty the earliest, followed by Latinas, Caucasians, and then Asians. In addition, girls whose mothers start puberty early are also more likely to start puberty early.
- Having a high body mass index (BMI)-for-age. Girls in the 85th percentile and above tend to start puberty earlier, whereas those in the 5th percentile or below typically start puberty later.
- Social and psychological stress. Researchers have found that family relationships may affect the timing of menarche.

CHAPTER 2

CYGNET:
Epidemiology, Puberty, and the Environment

The BABCERC's Epidemiology project is investigating how genes, the environment, biology, lifestyle, socio-economic factors, and body composition, separately and together, influence the age that puberty begins.

To explore this question, we started our Cohort Study of Young Girls' Nutrition, Environment, and Transitions (CYGNET Study), which is following 444 girls as they transition through puberty. Two of the other Breast Cancer and the Environment Research Centers are working cooperatively with the BABCERC on the study, which is one of the most comprehensive studies of environmental influences on puberty ever conducted.

Girls were eligible for the CYGNET Study if they were 6 to 7 years of age, spoke English or Spanish, and were both born in and were currently members of Kaiser Permanente of Northern California. Annually, we ask the girls' parents or guardians questions related to environmental, lifestyle, psycho-social and community factors that may affect when puberty begins. These questions address the girls':

- age, race, family structure, and household characteristics
- family income and environment
- diet
- physical activity
- use of personal care and household products
- chemical exposure
- health history
- residential and school history
- psycho-social development and behavior

When our epidemiologists began designing the CYGNET Study, they were aware that recent studies had suggested that psycho-social factors, such as a stressful family environment and the absence of a biological father, might also influence at what age girls start their periods. Including questions about family structure, household characteristics, psycho-social development, and behavior allows our researchers to further explore these previous findings. It also allows us to investigate whether these factors may also influence breast development.

Our Research Questions

The Epidemiology project is exploring questions such as:

- **Is the onset of puberty occurring in girls today earlier than it did in past generations?**
- **What environmental factors influence when puberty occurs?**
- **Do exposures to chemical compounds that influence female hormones affect the age at onset of puberty?**

CYGNET is one of the most comprehensive studies on environmental influences on puberty ever conducted.

We are collecting data from the girls':

- **Eating and exercise habits.** We have asked parents and guardians to provide information about what the girls have eaten in the past 24 hours, and have had the girls wear a pedometer, which measures the number of steps a person takes in a day. We are also asking them to tell us how much of this food is organic, which allows us to investigate whether eating organically grown and produced foods, which are less likely to contain hormonally active environmental chemicals, has an effect on puberty.
- **Blood and urine samples.** We use these for biomonitoring—to determine the girls' exposure to various chemical compounds that may be linked to pubertal development. When possible, we compare levels of chemical exposures in the CYGNET girls with national data collected by the National Health and Nutrition Examination Survey.
- **Saliva samples.** We use these to study the girls' DNA and their possible genetic susceptibility to early puberty.

We also regularly measure the girls':

- height and weight
- waist and hip measurements
- body fat
- breast and pubic hair development

What Is Epidemiology?

Epidemiology is the branch of medical science that developed from the study of epidemics of infectious disease in populations. It has since been expanded to study the nature of all sorts of diseases and conditions, whether infectious or otherwise.

Epidemiology is the science behind biomedical research, and it allows us to identify and investigate risk factors for specific diseases. This can be done by following groups of people over time, or by identifying the exposures, or preventive measures, that differentiate people who develop a disease from people who do not.

Epidemiologists also investigate whether the rates of diseases are increasing or decreasing in a population as well as whether certain interventions can prevent a disease from occurring.

We are charting these measurements because body size (height and weight/BMI) is known to affect when a girl starts puberty, with girls who are taller and heavier being more likely to enter puberty at a younger age. In addition, studies have shown that adolescents who remain overweight as they enter adulthood and continue to be overweight throughout their adult lives are at greater risk of developing postmenopausal breast cancer.

We are also investigating whether there is a relationship between girls' neighborhoods and their physical activity levels and BMI. Currently little is known about how neighborhood factors—such as crime rates and access to parks, playgrounds, and stores that stock healthy foods—affect exercise and eating habits and, in turn, pubertal development.

We look forward to sharing with the community the information that we learn from following the 444 girls in the CYGNET Study as they move into adolescence.

The CYGNET STUDY

There are 444 young girls enrolled in CYGNET. The racial and ethnic breakdown of the group is as follows:

RACE/ ETHNICITY	NUMBER	PERCENT
Latina, Hispanic	107	24
Black, non-Hispanic	96	22
Asian	49	11
White, non-Hispanic	182	41
Other	10	2
TOTAL	444	100

Calculating a Girl's Body Mass Index (BMI)

BMI is a number calculated from a person's weight and height, and it is used to determine whether a person's weight is healthy. For children and teens, BMI is age- and sex-specific and is often referred to as BMI-for-age.

BMI does not measure body fat directly, but research has shown that BMI correlates with direct measures of body fat. After a child's BMI is calculated, the BMI number is plotted on the CDC's BMI-for-age growth charts to obtain a percentile ranking. These percentiles are the most commonly used measure to assess children's growth patterns and to identify possible weight problems. An online children's BMI-percentile-for-age calculator can be accessed at http://www.kidsnutrition.org/bodycomp/bmiz2.html.

CYGNET STUDY TEA TALKS

One of the challenges of conducting a longitudinal study is keeping the people who have enrolled in the study interested and involved. Our Tea Talks, which are held twice a year, have played an important role in this effort. Hosted by our Community Outreach project, the Tea Talks provide CYGNET Study girls and their parents and guardians with an opportunity to interact with other study participants and their families, and to speak with the study staff and researchers in a non-clinical setting.

At each event, the girls take part in a special activity while the adults meet and discuss science and health topics related to the CYGNET Study, such as parenting pre-teens, the importance of exercise during childhood and adolescence, talking to girls about puberty, and the methods that scientists use to study environmental exposures. These discussions have been led by CYGNET Study investigators, including Drs. Julianna Deardorff, a psychologist at UC-Berkeley; Louise Greenspan, a pediatric endocrinologist at Kaiser Permanente San Francisco; Barbara Sternfeld, a senior research scientist at Kaiser Permanente; and Gayle Windham, a reproductive epidemiologist at the California Department of Public Health. Each Tea Talk ends with an awards ceremony, where the girls receive certificates in recognition of their involvement.

CYGNET Moms Say

"The main reason I come to Tea Talks is to bring my daughter, so she can meet and interact with other people in the program and to learn more about what the study is about."

"I like to be more aware of what my daughter is going to go through. It makes it easier for me as a mother of a girl to understand and know how to talk to her to make her more aware and what to expect when she reaches puberty."

MEET DR. JULIANNA DEARDORFF

Julianna Deardorff, PhD, is a co-investigator on the Epidemiology project. She is a psychologist in the School of Public Health at the University of California, Berkeley.

Q: Why were you interested in joining the BABCERC?

A: I've always been interested in the health effects associated with early puberty for girls, and being involved with the BABCERC has given me the opportunity to work with a diverse group of researchers to better understand why puberty appears to be starting earlier among girls in the U.S. I was thrilled to become part of an endeavor that not only brings scientists from different backgrounds and disciplines together but also consistently works to bridge the gap between researchers and the community.

Q: Why would family relationships affect the timing of menarche?

A: There is clear evidence that family relationships impact the timing of puberty among girls. Studies have shown that girls who have a warm relationship with their parents and who live with their biologically related fathers tend to start puberty later. We're not yet sure why this is, but the research now taking place should help us answer this question in the near future.

Q: What are some of the risk factors for early puberty and breast cancer that adolescent girls and their parents and guardians should be aware of?

A: I think the most obvious modifiable risk factor for early puberty is body weight. We know that girls who weigh more enter puberty earlier. Weight is also important to consider because some studies have shown that women who are overweight at certain points in their lives may be at greater risk of developing breast cancer. It's important for parents and guardians to teach and encourage girls to be physically active and to eat a well-rounded diet.

CHAPTER 3

Community Outreach and Translation: *Disseminating and Explaining Our Findings*

The BABCERC's Community Outreach project, known officially as the Community Outreach and Translation Core, serves as a liaison between the community and scientists. Composed of representatives from the Alameda, Marin, and San Francisco Departments of Public Health as well as from community-based organizations and breast cancer survivor programs, our Community Outreach project develops and implements strategies to:

- Bring the community's voice to the research process
- Translate the scientific findings into meaningful information for the public and policymakers
- Determine whether these strategies are effective

From the outset, the BABCERC has been dedicated to implementing a community-based participatory approach to studying breast cancer and the environment. We believe this approach will help foster trust between the community and our researchers, provide the community with the opportunity to play a significant part in the research process, and enhance the relevance of the research findings to the Bay Area.

Members of our Community Outreach project have worked closely with our Basic Science and Epidemiology projects to:

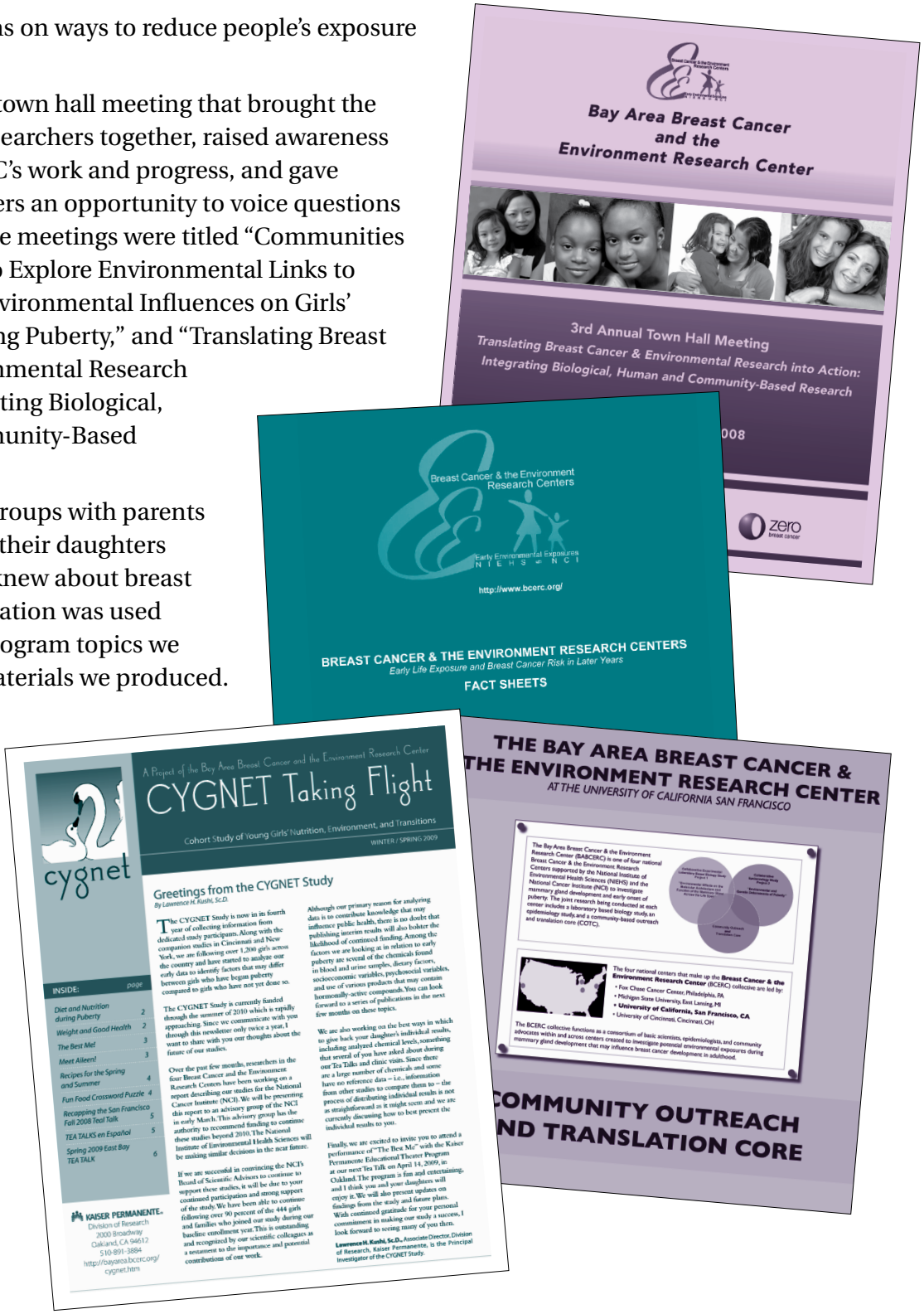
- Hold public meetings that provided opportunities for researchers to learn about the community's breast cancer concerns, interests, and research priorities.
- Select and prioritize which environmental exposures would be analyzed in the biospecimens obtained from the girls and to develop fact sheets on the compounds being investigated.
- Help ensure that the CYGNET Study girls and their families stayed in the study. As a result of these efforts, more than 90 percent of the girls who started the study continue to be involved four years after its inception.
- Communicate research findings to the girls' families.
- Co-author scientific and lay publications and abstracts that are made available to the public and policymakers.
- Use the research findings to develop educational messages about ways to reduce breast cancer risk.
- Collaborate with the Basic Science and Epidemiology projects to develop the research agenda to ensure that a community perspective was integrated into the initial grant proposal.
- Help researchers develop projects that reflect the community's concerns.

Our Community Outreach project developed materials and programs designed to keep the community informed on our progress and findings. Our activities included:

- Writing articles for our newsletter and a white paper summarizing the history of the use of polybrominated diphenyl ethers (PBDEs) in California, after our data unexpectedly showed that the CYGNET girls had higher levels of PBDEs than did other girls in a national study. We also developed a fact sheet on PBDEs that

includes suggestions on ways to reduce people's exposure to these chemicals.

- Hosting an annual town hall meeting that brought the community and researchers together, raised awareness about the BABCERC's work and progress, and gave community members an opportunity to voice questions and concerns. These meetings were titled "Communities Coming Together to Explore Environmental Links to Breast Cancer," "Environmental Influences on Girls' Development During Puberty," and "Translating Breast Cancer and Environmental Research Into Action: Integrating Biological, Human, and Community-Based Research."
- Conducting focus groups with parents and caregivers and their daughters to learn what they knew about breast cancer. This information was used to determine the program topics we selected and the materials we produced.
- Planning the BCERC's annual scientific conference on early environmental exposures.
- Disseminating educational and outreach materials to the news media, on our Web site, at scientific and public meetings, and at local events.



MEET JANICE BARLOW

Q: Why were you interested in being part of the BABCERC?

A: Zero Breast Cancer focuses on identifying environmental factors and the role they play in the development of breast cancer at all stages of life. This project was a perfect fit for us, as this grant offered a unique opportunity to study the environment in a systematic way and to work collaboratively with top researchers and other breast cancer organizations.

Q: What have you learned from being a leader in community-based participatory research?

A: The participatory process enhances research, makes the process more responsive to a community's needs, and increases the likelihood that we will find answers and solutions. Everyone involved in this project shares the same ultimate goal: to create change in our communities, through education or public policy, that will reduce breast cancer incidence.

Q: As a breast cancer advocate, what do you want researchers to understand about this project?

A: I think it is important for researchers to understand what the community wants and how the community tends to think about the research process. Researchers can deal with more uncertainty because it is part of a culture of science in which research findings must be replicated, and where new findings are seen as incrementally adding more information. The public, in general, has less tolerance for uncertainty. They want the research to tell them what to do and how to solve the problem—but science can't always do that.

Q: What has been the most interesting part of this project for you?

A: Working with both the Epidemiology and Basic Science projects has allowed me to see how complex breast cancer really is. There are so many different variables involved in the development and initiation of breast cancer, from tiny molecules to the social environment. I now have a much better understanding of how the normal mammary gland develops, how similar this process is to cancer, and why understanding what goes wrong in the normal process can help us understand how cancer develops.

Janice Barlow, MSN, CPNP, heads the Community Outreach project. She is the Executive Director of Zero Breast Cancer, a nonprofit organization dedicated to finding the causes of breast cancer through community participation in the research process.

CHAPTER 4

What We Are Learning

Over the past five years, the BABCERC has contributed in important ways to the breast cancer field. Our findings have been published in numerous articles in an array of scientific journals, presented at local and national breast cancer conferences, and discussed at town hall meetings. We have also developed educational materials for the community on topics ranging from environmental chemicals to the Tanner staging system, which epidemiologists and clinicians use to chart a girl's progress through puberty.

Our Basic Science Project's Findings

The BABCERC's Basic Science project has developed and implemented innovative scientific techniques that researchers can use to identify certain key genetic regulators and protein signals that control the mammary development during puberty and that result in the development of the breast ducts. These techniques have already led to novel findings, and we will continue to use them in future studies examining how environmental carcinogens stimulate breast cancer cells.

Applying these techniques to cells found in the mammary glands of mice that have gone through puberty, we have learned that:

- Mice that lack an enzyme called DGAT1, which is required for the mammary gland to develop properly, are unable to produce milk. They also have abnormal lipid levels in their supporting cells, which increases their risk of breast cancer. This suggests that levels of DGAT1 may be related to breast cancer risk.
- A gene called GATA-3 must be active for the luminal epithelial cells to grow and develop during puberty. This is interesting because scientists studying breast cancer have found that women whose tumors have high amounts of GATA-3 have a better outcome than women whose tumors have low amounts of GATA-3, who are more likely to have a breast cancer recurrence. We also showed that replacing the GATA-3 in low GATA-3 mice stopped their metastasis. These findings may help us develop new early detection and treatment strategies.
- Mice that lack a gene regulator called C/EBPß, which makes a molecule that regulates a cell's life cycle, also lack a molecule, called E, that controls cell growth. This provides us with more information on how breast cancer disrupts the normal cell cycle and gives us insights into molecules that might be targets for new breast cancer prevention treatments.
- The ends of chromosomes are protected by special structures called telomeres. When telomeres do not function properly, chromosomes can be damaged by the body's own DNA repair pathways, leading frequently to the death of host cells but sometimes to mutations observed in cancer cells. This has led us to hypothesize that telomere dysfunction plays a role in the generation of pre-malignant cells from normal cells. We are currently investigating how x-rays and other environmental factors influence telomere dysfunction.
- The epithelial cells in the breast ducts produce a protein called amphiregulin (AREG), and fibroblasts, which have mammary epidermal growth factor receptors, respond to this protein. However, before the fibroblasts can get a

message from AREG, a third molecule, called ADAM17, must first release AREG from the layer of tissue where it is produced. This helps explain how these three molecules regulate mammary growth, how the different cell types talk to each other through these molecules, and why they are important in breast development.

- During puberty, 1,074 genes increase at the tip of the growing mammary gland bud, and 222 genes increase in the surrounding tissue. The new techniques we developed enable us to pinpoint precisely where in the mammary gland these genes are expressed, and give us new ways to think about developing treatments to target the specific genes that are fueling cancer growth.
- A time-lapse photography/video method we developed allows us to see that the mammary ducts branched only when crucial proteins, called growth factors, were close by. We also discovered that this branching takes place only in special sites that have multiple layers of tissue. This is significant because similar multiple layers of cells are an early event in breast tumor formation. We intend to use this new video method in future studies.
- We developed a new way to infect mammary epithelial cells (the cells which line the breast ducts and from which breast cancers arise) with a virus that contains a specific gene we are interested in studying. Our new method is more practical and effective than the existing approach, and our findings support the current theory that many mammary branches can arise from a single breast stem cell and that several different stem cells can contribute to the formation of a single duct. This helps us understand both how the breast ducts develop and how a breast tumor begins to form.

CYGNET Study girls at a recent Tea Talk.

These new techniques also allow us to study breast cancer stem cells and to map their location in the mammary gland. Our findings suggest that:

- A carcinogen can increase the number of stem cells found in the mammary glands of mice exposed to radiation during puberty. This is significant because it is believed that breast stem cells are the cellular targets of carcinogens. We are now investigating which specific signals regulate these stem cells and how carcinogens may interfere with this process.

We have also investigated precisely how carcinogens affect breast cells. These studies have taught us that:

- Disrupting normal tissue by exposing it to ionizing radiation promotes tumor formation. This suggests that we may be able to control

The participatory process makes research more responsive to the community's needs

Disseminating research findings at an annual town hall meeting.

cancer cells by monitoring the tissue in their immediate environment.

- Ionizing radiation alters the tissue's micro-environment, which, in turn, promotes mammary carcinogenesis, perhaps by disrupting the way in which breast cancer stem cells are regulated. It has previously been suggested that radiation results in cancer by directly damaging DNA. This finding gives us a new way to think about how breast cancer develops, how environmental factors increase breast cancer risk, and how we can prevent breast cancer from occurring.
- A specific type of inflammatory cell, called a mast cell, promotes the growth of new blood vessels after exposure to ionizing radiation. We also showed that when we added molecules that inactivated the mast cells, no new blood vessels grew. This finding is important because it suggests that mast cells are necessary for a tumor to grow.

We have further explored our new model of cancer as a "phenomenon of tissues" rather than just abnormal single cells. We believe this more accurately describes how cancer develops. We showed that:

- The breast tissue of mice exposed to radiation looks disorganized and has excessive cell growth, whereas the breast tissue of mice not exposed to radiation is one-half to one-quarter as likely to show abnormal growth. This is exciting because preliminary reports suggest that restoring the health of the tissue that surrounds a cancer may prevent the cancer from spreading.
- In experiments in which supportive tissue is treated with a cancer-causing agent, tumors develop in the adjacent cells not treated with the carcinogen. This suggests that by monitoring the state of the tissue surrounding cancerous cells, we may able to predict whether the tumor is getting ready to spread.

Our Epidemiology Project's Findings

The BABCERC's Epidemiology project has been following the CYGNET girls for four years. Because this study is being conducted cooperatively with two other Breast Cancer and the Environment Research Centers, we are able to compare our findings as well as pool our data with theirs to answer questions about national trends and chemical exposures.

Our pilot studies and preliminary analyses have shown that:

- Girls are entering puberty earlier than recent studies have suggested. Data from the Third National Health and Nutrition Examination Survey (NHANES III), which took place between 1988 and 1994, showed that girls were beginning puberty—as indicated by breast budding—on average, at age 10.4 for non-Hispanic whites, and 9.5 for non-Hispanic blacks. Preliminary data from all three centers shows that girls in our studies are beginning puberty at an average age between 9 and 10 years of age.
- Preliminary data on urinary excretion levels of selected environmental chemicals in CYGNET girls found a wide spectrum of hormonally active biomarkers detectable in the girls' urine and blood. Levels of some of the chemicals varied depending on the girls' race/ethnicity and body mass index, and this may be relevant to puberty and breast development. These results show us that chemical compounds that may influence hormone metabolism and puberty are detectable in girls' urine, and that data analyses conducted on a larger number of CYGNET girls are likely to provide important information about environmental chemical exposures.
- About 30 percent of the girls are overweight, based on their current BMI measurements. We will be investigating whether girls who are overweight have different exercise or eating habits, are more likely to mature more rapidly, and have different levels of exposure to chemical compounds.
- There are substantial maturation differences in our girls based on race/ethnicity, with 32 percent of African-American girls showing the first signs of breast development or pubic hair at baseline (age 6–7); 15 percent of Hispanic girls, 10 percent of white girls, and 4 percent of Asian girls had reached a similar stage of development.
- A girl's BMI at 6 to 7 years of age is a major predictor of when she will begin to develop breast and pubic hair. This finding confirms previous research that has shown a relationship between BMI and pubertal development.
- Girls who showed evidence of earlier onset of breast development were more likely to have a diet high in animal protein and sugar and low in vegetable protein, fiber, and phytoestrogens.
- Our CYGNET Study girls had higher blood levels of PBDEs than did girls in the Ohio cohort. Our girls' levels were also higher than those in adolescents (aged 12–19) enrolled in NHANES III. Studies have also found higher rates in adults in California than other states. Animal studies suggest PBDEs may disrupt thyroid and reproductive function. Furthermore, other studies have shown that over the past decade, levels of PBDEs have been rising in the environment in the U.S. California is believed to have high levels because of its history of more stringent flammability standards, which were met by adding PBDEs, flame retardant chemicals, to foam and furniture.
- Fat intake per se does not appear to influence when girls start puberty. However, girls who ate a more plant-based diet had a lower likelihood of having earlier breast development. This is consistent with studies that have shown that adults who have a lower fat intake and eat more dietary fiber have lower levels of circulating free estradiol. It is also of interest because mouse and rat studies have shown that high-fat diets increase breast cancer risk.

BABCERC members address audience questions at a recent town hall meeting.

Our Community Outreach Project's Findings

The BABCERC's Community Outreach project created and implemented programs and materials that are critical to our commitment to conduct community-based participatory research. Project members also conducted a study that investigated how our approach influenced the Basic Science and Epidemiology research projects and to what extent we successfully met our goals. This study will help others identify factors that can facilitate or hinder the participatory research process. Our study showed that:

- BABCERC members believe that our work on this project is closely aligned with the guidelines of participatory research.
- Participatory research increases community understanding and support of the scientific process. As one community member said, "I could really see the community benefit from what was found. What did they discover? Is it something we can work on, something that can be utilized for generations to come?"
- Opportunities for meaningful community input are easier to provide in epidemiologic research than in basic science.
- Community participation heightens the sensitivity and propriety of the research. As one project member noted, it was not unusual for members to ask, "Is this appropriate for a 7-year-old girl? What's a mother going to think?"
- A participatory approach improves the communication and sharing of knowledge between scientists and community advocates. As one BABCERC researcher pointed out, "The truth is, scientists have expertise and skill that advocates don't. But advocates have insight and a perspective that scientists don't. And it's really about mutual understanding. Having both perspectives is really valuable."

CHAPTER 5

Next Steps

When we formed the BABCERC, the "windows of susceptibility" hypothesis had only recently been introduced, and only a small number of researchers were investigating whether environmental exposures during childhood might influence the onset of puberty and breast development. Even fewer were looking at whether exposures that occur during puberty might alter the risk of breast cancer later in life.

We are proud to have been—and to continue to be—leaders in the effort to focus research attention and public health policies on these issues. We believe that by broadening the focus of research on breast cancer and the environment to include children and adolescents, we have the potential to gain new insights into what causes breast cancer to occur and how early exposures to carcinogens may affect breast tissue in ways that increase breast cancer risk in adulthood.

Future Plans

Over the next year, our three projects will continue to work together to shape and expand our research agenda. One of our top priorities is to obtain the funding necessary to continue all three projects. Currently, only a small percentage of our CYGNET Study girls have begun menstruating. Additional funding will allow us to follow all our girls as they move through puberty and young adulthood and to continue to investigate possible links between early sexual maturation, environmental exposures during puberty, weight, and breast cancer risk.

Moving the Science Forward: Our Aims and Goals

Our work is just beginning. Our research findings are still coming in, and what we have learned has led to new questions—which tells us we are on the right track. Our aims and goals include:

- Identifying the environmental agents that can damage breast cells during windows of susceptibility.
- Developing cell culture models with human breast cells to learn important aspects of human pubertal development.
- Learning more about how cancer develops in the epithelial cells that line the breast ducts and what role the surrounding tissue plays in cancer development.
- Gaining more insights into the extent to which puberty is a window of susceptibility to environmental carcinogens and the potential ramifications of our findings.
- Analyzing the DNA we have collected from the CYGNET Study girls to see if we can identify any

What Girls Can Do Now: Tips for Parents and Caregivers

- Help and encourage girls to maintain a healthy weight.
- Make sure girls get regular exercise during or after school.
- Avoid using plastic products where possible.

gene variants related to puberty.

- Conducting focus groups with the parents and guardians of CYGNET Study girls to learn what type of information they would like to receive about individual-level results of the girls' environmental exposures and determining the best ways to provide these results.
- Examining whether new chemicals or chemicals that have not previously been studied have an effect on breast development when they are added to the exposures the girls already have.
- Using our animal and tissue models to investigate whether certain exposures affect only certain parts of the breast gland or certain cell types.
- Exploring the effect that obesity has on the endocrine system as well as possible interactions that may occur between obesity and exposure to endocrine-disrupting chemicals.
- Learning more about phthalates and phenols and the effect they may have on the pubertal transition in girls.
- Learning more about the role of inflammation in breast cancer development.
- Disseminating information about the BABCERC, our research, and our findings nationally.
- Strengthening the BABCERC's relationships with local, regional, and national breast cancer advocacy and environmental advocacy organizations.

What You Can Do Now: Seven Ways Women Can Reduce Their Breast Cancer Risk

- Minimize radiation exposure
- Minimize alcohol intake
- Avoid active and secondhand exposure to tobacco smoke
- Avoid exposures to exogenous estrogens, including hormone replacement therapy and hormonally active environmental chemicals
- Lengthen the duration of breastfeeding
- Maintain leanness or reduce weight
- Increase participation in exercise activities

We are proud to serve as a model for community involvement in cancer research. We hope our efforts will encourage other researchers to expand community participation in the research process. We look forward to updating you on our progress.

10 SUGGESTIONS TO REDUCE YOUR EXPOSURE TO SUSPECTED CHEMICALS

- Use glass containers in the microwave.
- Ask for dry cleaning services that do not use PERC, or ask for "wet cleaning."
- Take time to read labels and avoid phthalates and "fragrance" in products.
- When grilling food, minimize "char" by reducing the heat level and/or using marinades.
- Purchase organic foods when possible and encourage stores you patronize to expand their selection of organic foods.
- Monitor what chemicals are put down the drain in your home.
- Remember that not all vacuum cleaners are created equal. Get one with strong suction, a multilayered bag for dust collection, and a HEPA filter.
- Look for electronic equipment and furniture without PBDEs.
- Use organic practices for gardening and lawn care and encourage your neighbors to do the same.
- Encourage your town to adopt policies of using natural and non-toxic solvents in public buildings and organic practices in the care of green spaces.

Online Resources

Visit these Web sites to learn more about the potential health effects of common household and occupational products.

- Household Products Database
  www.householdproducts.nlm.nih.gov
- Toxics Release Inventory and Superfund maps
  www.toxmap.nlm.nih.gov
- Haz-Map Database
  www.hazmap.nlm.nih.gov
- Campaign for Safe Cosmetics
  www.safecosmetics.org

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