Testimony
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Committee on Energy and Commerce
United States House of Representatives

NIH Research on the Role of the Environment in Breast Cancer Development and Progression

Statement of

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Thank you for the opportunity to speak to you today. I am Deborah Winn, the Associate Director for the Epidemiology and Genetics Research Program at the National Cancer Institute (NCI) within the National Institutes of Health (NIH), an agency of the Department of Health and Human Services. I specifically oversee research seeking to identify environmental and genetic factors involved in the etiology of breast cancer, which H.R. 1157, the "Breast Cancer and Environmental Research Act of 2007", also is intended to address. We at NIH believe that the Public Health Service Act, as amended by the NIH Reform Act of 2006, provides sufficient authority to address this area of research, as well as others. As science advances through discovery, it increasingly converges. We know that the answers to the most vexing scientific questions involving one disease often come from areas of unrelated research. As scientists, we know that it would be a mistake to focus on one disease without understanding the underlying biological mechanisms that affect multiple diseases. This is one of the great lessons learned from recent advances in genomics and molecular biology.

These lessons should apply to well-intended legislation, as well. In general, prescribing a specific way of conducting Federal research could have the unintended consequence of narrowing the field of inquiry and promoting an unwise use of precious resources. We must be careful to avoid such unintended consequences in the consideration of any bills, particularly those aimed at specific diseases.

As you deliberate, I want you to know about our progress in understanding the role of the environment in the development and progression of breast cancer in the hope it will illuminate your understanding of the issues under consideration at today's hearing.

It is estimated that 182,460 women will be diagnosed with breast cancer in 2008, and 40,480 women will die of cancer of the breast in 2008. Known risk factors include increasing age, family history, reproductive history, obesity, heavy alcohol intake, and hormonal replacement therapy. We know less about possible environmental causes of breast cancer, but we recognize that breast cancer is a complex disease caused by multiple interacting factors, including genes, hormones, and environmental exposures, that interact across the lifespan and may share common etiologic pathways with other cancers and diseases.

The NIH estimates that it will fund $705 million in breast cancer research in FY 2008, representing a robust research portfolio covering etiology, prevention, early detection, diagnosis, treatment and rehabilitation. Within the portfolio, we expect $60.7 million will be specifically spent on researching the role of the environment in breast cancer development at NCI, and $35 million will be spent at the National Institute of Environmental Health Sciences (NIEHS), totaling almost $100 million in support of this important area across NIH.

Despite this substantial investment, well-conducted studies of adult women have revealed little in the way of findings of possible environmental causes of breast cancer. Therefore

investigators are taking a fresh approach to this problem and have shifted their focus to studying "windows of susceptibility". "Windows of susceptibility" are the prime events over the life span where exposures to environmental factors can directly or indirectly affect a person's risk for developing breast cancer. This approach stems from the knowledge that there are specific windows of time that physiologic changes to the mammary gland occur. These include gestation, puberty, pregnancy and lactation. Exposures that occur during these periods of time early in life may influence the risk of developing breast cancer. Narrowing in on these specific time periods will improve our understanding of the interactions of genes, the environment, and cancer risk.

Breast Cancer and Environment Research Centers

To uncover the links between early environmental exposures and cancer risk, NCI partnered with NIEHS in 2003 to fund four Breast Cancer and Environment Research Centers (BCERCs). These BCERCs are specifically focusing on exposures during early life and during puberty because they are important windows of susceptibility for breast cancer. Studies have consistently shown age at onset of menstruation to be a breast cancer risk factor. It is important to study the factors that affect the age at breast development too, since girls who go through puberty earlier will have a longer period of exposure to estrogen and may be at increased risk for breast cancer later in life.

The Research Centers are headquartered at Fox Chase Cancer Center in Philadelphia, University of California San Francisco, Michigan State University in East Lansing, and the University of Cincinnati in Ohio, but each Center is a consortium and has many other

research partners. The BCERCs were designed to include breast cancer advocates as foundational parts of each Center and the program as a whole. Breast cancer advocates play a unique role at each of the BCERCs. They contribute to the dialogue on scientific themes, provide outreach to the general public and families of study subjects and they are developing materials to educate the public on what we should know about the role of the environment in breast cancer risk. Advocates play an active role in the governance of the BCERC as formal members of various steering committees and an advisory working group.

The BCERCs have been instrumental in expanding what is known about the role of the environment in breast cancer research by using both animal models and studies in human populations. Animal models allow investigators to examine the entire reproductive span of the animals to understand how environmental factors influence breast cancer development. For example, animal models are being used to see if treatment with soy and other estrogen-like plant compounds during early life may influence the structure and function of the mammary gland as it matures and may protect the gland by making it less susceptible to chemical carcinogens.

The BCERC also includes an epidemiologic study following young girls through pubertal development. Scientists are studying environmental, psychosocial, dietary and other determinants of breast development and other components of puberty. Investigators at one Center have found preliminary evidence that many girls have detectable levels of hormonally active chemicals, and the relation of these levels to breast development are

being studied more fully to see if they delay or speed breast development. This cohort is being followed to determine which environmental exposures may be associated (either positively or negatively) with earlier breast development so that preventive strategies can be developed to reduce exposures during this critical period of development in order to reduce breast cancer risk in the future.

Recent stories in the news around exposures to a plasticizer, Bisphenol A (BPA) highlight the type of work in the BCERC that bring together basic and public health scientists and advocates. BCERC is studying a cohort of young girls, and preliminary findings show that girls across the study sites have detectable levels of BPA in their urine, and those girls who are not obese tend to have higher rates of BPA. These data have yet to be finalized. In addition, data on the association of body mass index (BMI), BPA, and timing of breast development is being studied in the BCERC study.

The BCERC program is in a unique position to facilitate the exchange of emerging scientific information between basic scientists, clinicians, and population scientists to expeditiously test hypotheses that emerge from the coordinated studies of chemicals such as BPA. Not only can scientific discovery be expedited, but the involvement of advocates in the project also allows for dissemination of these research findings to the public.

Our understanding of breast cancer is changing, as is our understanding of the environment. These changes are necessitating a shift in our scientific strategies for

studying risk factors for breast cancer. In addition to the BCERCs, we are using other innovative approaches, such as genome-wide association studies (GWAS) to understand breast cancer susceptibility. GWAS are a new and promising area of research to understand susceptibility to many different diseases including cancer.

Genome-Wide Association Studies

Genome-wide association studies (GWAS) involve a systematic look across the entire human genome to identify genetic variants that are associated with increased risk for both common and uncommon cancers. By scanning the DNA of thousands of breast cancer cases compared to DNA from healthy women, NCI investigators have recently identified genetic variants in a specific gene that are associated with increased breast cancer risk and are estimated to be present in more than 60 percent of U.S. female adults. Another unexpected and exciting finding is the discovery that a region on chromosome 8 is associated with breast, colon, and prostate cancers. These findings, along with several others from multiple studies, suggests that looking at these genetic regions in conjunction with behavioral, reproductive, dietary and environmental factors together can shed some light on common causal pathways to cancer development in general. The results of genome-wide studies, with the follow-on studies targeted at the identified genes, promise to provide novel strategies for detection and prevention, well beyond what can be learned from studies of single genes.

National Toxicology Program

Over the past decade, the National Toxicology Program (NTP) has conducted experimental laboratory animal studies at NIEHS that show that chemicals identified to cause mammary gland cancer in rodents are frequently mutagenic or show estrogenic properties. In total, over 40 chemicals have been identified as mammary gland carcinogens. These include phenolic chemicals that may be both weakly estrogenic and further metabolized to mutagens. Other classes of chemicals that were identified to cause mammary gland cancer in rodents include halogenated hydrocarbons, aromatic amino/nitro compounds and chemicals that can be metabolized to epoxides. Many of these carcinogens and other chemicals have been shown by NTP studies to be endocrine disrupting chemicals and may also increase susceptibility to breast cancer through hormonal pathways.

Genes and Environment Initiative

The Genes and Environment Initiative (GEI) is a four-year, NIH-wide program led by the National Human Genome Research Institute (NHGRI) and NIEHS that is supporting efforts to identify major genetic susceptibility factors for diseases of public health significance and to develop technologies for reliable and reproducible measurement of potentially causative environmental exposures. The GEI has two major components.

The genetics component is conducting GWAS using DNA specimens collected from on-going population studies of over a dozen major diseases in order to identify single gene variants that may be associated with risk. Complementary replication studies in other

populations and functional gene studies are also planned to validate the newly identified susceptibility genes.

The Exposure Biology Component is using a product driven approach to improving exposure assessment of commonly occurring exposures and lifestyle factors, such as chemicals, stress, addictive substances, diet, and physical activity. New biological and engineering technologies such as genomics, proteomics, global positioning systems (GPS) and spatial indicators, physiologic and chemical sensors, and image enhancements are being incorporated into new biomarkers or devices that will improve the characterization of these factors in human populations. The ultimate goal of the GEI is to look broadly at interplay between genes and environment to identify risks of disease.

The Exposure Biology program has several projects that directly address concerns about chemical exposures that may increase risk of breast cancer. These projects seek to develop new biomarkers of response to xenoestrogens by defining signatures of response in blood proteins and DNA methylation patterns in mammary gland tissues. These important projects will help better define the effects of exposure on breast cancer risk in women.

The Sister Study

The Sister Study, which NIEHS began in October 2004, is a unique long-term study of women aged 35 to 74 whose sisters had breast cancer. The study aims to uncover the links between genetics and the environment in the development of breast cancer using

epidemiological analysis and biochemical investigations of a cohort with about twice the risk of other women for developing breast cancer. The study is an unprecedented effort to understand the relative importance and interplay of genetic and environmental factors in the disease. The study is quickly approaching the goal of enrolling 50,000 diverse women, but to ensure the results benefit all women, researchers are focusing on increasing the number of participants from targeted demographic groups, such as African Americans, Latinas, Asians, Pacific Islanders, and Native Americans, as well as Caucasian women with high school degree or less, or who are between the ages of 65-74.

Recent funding from the Susan G. Komen for the Cure foundation will allow NIEHS scientists to conduct a family-based study. Called the Two Sister Study, its aim is to investigate the genetic and environmental factors that influence young-onset breast cancer—breast cancer developed before age 50. The study will include about 2,000 of the 50,000 women with breast cancer whose sisters enrolled in the Sister Study, along with their unaffected sister and genetic data from any parents who are still living.

The Sister Study team of partners includes many breast cancer organizations and advocacy groups. These groups include the American Cancer Society, NIH's National Center on Minority Health and Health Disparities, Sisters Network Inc., Susan G. Komen for the Cure, Breast Cancer Network of Strength (formerly known as Y-ME National Breast Cancer Organization), and Intercultural Cancer Council, and have been instrumental to the success in enrollment and follow-up of the study participants across the US.

The Polish Breast Cancer Study

Breast cancer is not just a domestic issue but a disease that exacts a heavy toll around the world. A global approach to research enables explorations of interactions between genes and specific environmental exposures found in diverse geographic settings. In a collaborative effort with researchers in Warsaw and Lodz, Poland, NCI investigators are conducting a population-based study to investigate a variety of potential risk factors, including tobacco, hormones, and occupational chemical exposures, and their interactions with genetic markers that may be important in breast carcinogenesis.

Conclusion

NIH funds research that takes a diverse approach to studying breast cancer and the environment. This approach includes identifying specific chemicals which change the structure and function of the mammary gland during different windows of susceptibility, understanding gene-environment interactions in the etiology of breast cancer and associated physiologic milestones that are associated with breast cancer risk. In addition this research is focused on identifying common pathways across different types of cancer. With the continued collaborations of scientists, advocates, and institutes, we are well-equipped to continue to support and enhance the area of breast cancer and environment research.