SILENT SPRING INSTITUTE

RESEARCHING THE ENVIRONMENT AND WOMEN'S HEALTH

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Everyday Exposures and Breast Cancer

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Thank you for focusing this year on environmental factors in cancer, a key arena for efforts to significantly change the cancer burden in this country through primary prevention of disease. I am pleased to have the opportunity to contribute to this dialogue. My remarks are grounded in my research about environmental factors and breast cancer and have particular relevance for other hormonal cancers as well – for example, prostate, testicular, ovarian, and endometrial cancers.

I begin with a thought experiment about the process of discovery in cancer etiology. This perspective underlies my recommendations for fundamental change in the evidence we use to find and attack the environmental causes of a disease like breast cancer. Then I will address what we know now about three biological mechanisms that may link environmental pollutants and breast cancer, and about human exposures to suspect chemicals. Finally, I discuss the critical next steps to act on and expand our knowledge.

What evidence can we rely on to learn about causal relationships as a basis for prevention?
Starting with an easy example of public health evidence, how do we know the gunshot killed the victim? The evidence is observational, not experimental; but we may see the entire causal pathway. The gun was raised and fired, the bullet entered a vital organ, and the victim fell to the ground. Or perhaps no witness saw the gun, but the bullet was found and matches the wound.

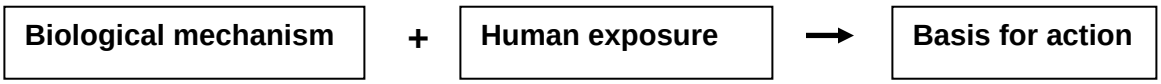
Now suppose the "gunshot" is polycyclic aromatic hydrocarbons (PAHs) – products of combustion found in vehicle exhaust and air pollution, tobacco smoke, and grilled food. The question is whether this exposure causes breast cancer. We can't see this gunshot, though we can detect it with expensive laboratory tests. It may have been fired 20-60 years before a breast cancer is apparent. The bullet didn't enter the body through the breast. It occurs in conjunction with a lifetime of other contaminants. This gunshot doesn't always kill – only a fraction of exposed women are affected. And the cause and effect picture is harder to discern because many breast cancers occur for other reasons. With this kind of gun, we have a difficult detective job indeed.

In medicine, we solve some of the difficulties with a clinical trial, which specifies aspects of the causal equation under study. We test whether drugs are safe and effective by randomly assigning patients to two equivalent groups, giving half of them a predetermined dose and then watching to see whether the health outcomes in the two groups differ. Participants undertake risks, because they hope for benefits. Using this method, the Women's Health Initiative (WHI) unexpectedly revealed that hormone replacement therapy (HRT) increases cardiovascular risk as well as breast cancer. Women went off HRT after the WHI report, and several studies now indicate that breast cancer incidence dropped in older women as a result. What might be the parallel influence of hormonal exposures from consumer products and pollution? We can't answer that question the same way, because we wouldn't do this kind of experiment for environmental pollutants and chemicals in consumer products. It would be unethical to expose half of a group of girls or women to a possible toxic chemical to see what happens.

Thinking about these scenarios, we see that environmental breast cancer studies involve exposures over years and decades to unseen chemical mixtures with different effects in different women. In the face of this challenge, we cannot give up, though; because the stakes are too high. Breast cancer remains the leading cause of death in women from their late thirties to early fifties, years when their children are at home. Treatments have improved but will likely remain arduous and debilitating. Most importantly, the

promise of prevention is enormous. The high risk BRCA1 and BRCA2 mutations account for just 5-10% of breast cancers, and a large study of twins estimates that known and unknown inherited genes explain just 27% of breast cancer risk.[1] In citing this statistic, I do not imply a dichotomy of genetic versus environmental causes. We must recognize the interplay of genes and environment in all cases; but the evidence does tell us to focus much more on the environment side of this equation.

To move forward, we must stop allowing medical research paradigms -- which are based in human clinical trials and epidemiologic studies where you can see or ask about exposure – to impede progress in environmental health. We must stop allowing statements that there is "no proof that A causes B" to block action based on the weight of evidence that we do have.[2, 3] Instead, we must build an environmental health paradigm for long-latency disease in which we rely on animal and cell studies of biological mechanisms coupled with human exposure studies, using these types of evidence as a basis for public health intervention to reduce exposure.[4] Epidemiologic evidence is expected to lag behind, while we act judiciously on early warnings from studies that show a chemical affects cancer mechanisms in animals or cells, and that people are substantially exposed.



Environmental pollutants and breast cancer: What do we know now?

If we adopt this paradigm, we see substantial evidence of links between environmental pollutants and breast cancer, enormous knowledge gaps that we can fill immediately, and opportunities for precautionary action. I led a team of researchers from Silent Spring Institute, Harvard University, Roswell Park Cancer Institute, and the University of Southern California that reviewed much of this scientific literature in *Cancer*,[5] a peer-reviewed journal of the American Cancer Society, and in an online database,[6] which was selected as a "top pick" by *Science*.[7] This project was supported by Susan G. Komen for the Cure.

Laboratory evidence supports at least three biological mechanisms that may link environmental pollutants and breast cancer: (1) chemicals that cause mammary gland tumors in animals are predominantly mutagens, acting as classic carcinogens that damage DNA; (2) chemicals called endocrine disrupting compounds (EDCs) mimic or block hormones, including estrogen, a known breast cancer risk factor; (3) developmental toxicants can divert development of the mammary gland in ways that permanently increase susceptibility.

The chemicals that show these types of biological activity are ubiquitous environmental pollutants and common in workplaces, consumer products, and building materials. Before I discuss examples, though, let me emphasize that most chemicals in use today have never been tested for these effects.[8]

Turning to chemicals that *have* been tested in animal cancer bioassays, 216 chemicals caused mammary gland tumors.[9] About 100 are common exposures: 73 have been present in consumer products or as contaminants in food, 35 are air pollutants, 25 have been associated with occupational exposures affecting more than 5,000 women a year, 29 are produced in the United States in large amounts, often exceeding 1 million pounds per year, and 47 are pharmaceuticals. Examples of mammary carcinogens include PAHs (the invisible "gunshot" I mentioned earlier); mutagen X, a contaminant in chlorinated drinking water; benzene, which is in gasoline; ethylene oxide, a common sterilant in healthcare and food processing; methylene chloride, an industrial solvent; and many pesticides. A recent study by Kaiser supported the relevance of the animal model to humans, finding that 3 of 6 pharmaceuticals they evaluated from our list increased incidence of breast cancer in women taking those medications.[10]

Estrogen mimics, chemicals that make human breast cancer cells proliferate in the laboratory, include bisphenol A, the topic of numerous news stories this year about baby bottles, toys, sports water bottles, food can liners, and other products; many pesticides, and compounds in cleaners and personal care products, like hand lotions and make-up. EDCs are now common pollutants in surface water and groundwater that supplies drinking water.[11, 12]

For endocrine-mediated developmental toxicants, diethylstilbestrol (DES) is an important cautionary model. We learned tragically that a mother's exposure during pregnancy increases cancer risk, including breast cancer, in her offspring. Animal studies show stunted mammary gland development and increased susceptibility to mammary carcinogens following *in utero* exposure to the EDC dioxin, and evidence of similar effects on mammary gland development is accumulating for additional chemicals, including the pesticide atrazine, widely used in the US. [13, 14] Research showing that low doses of chemicals can distort development is one of the most troubling and rapidly growing fields of science.[15]

The *National Report on Human Exposure to Environmental Chemicals*[16] is the best source of information on the typical exposure to environmental pollutants in the US population. This resource is how we know that public health measures to reduce exposure to lead and environmental tobacco smoke are working. The study has tested for about 15 of the animal mammary gland carcinogens and for selected EDCs, including, for example, some pesticides and phthalates, dioxins, polychlorinated biphenyls, and brominated flame retardants. Because government has been so slow to address the health effects of environmental pollutants, a number of advocacy organizations have tested for these and additional chemicals in children and adults across the country. Results show that all of us carry residues of numerous toxic chemicals in our bodies, often at levels shown in other studies to be biologically relevant.

My own research team has focused on understanding where these exposures come from through our study of 89 EDCs in 120 suburban and rural homes, located far from industry and in mostly nonagricultural areas.[17] For 30 of the chemicals, this was the first report on levels indoors. We found 67 different EDCs and the average home indoor air sample contained 19 different compounds. We found 27 different pesticides in house dust and indoor air. EDCs from sources like laundry detergent and cosmetics were among the most abundant chemicals detected and were found in nearly every home. We found DDT, banned in 1972, in two thirds of the homes. The mundane ways in which high exposures arise is illustrated by our case studies of PCBs and brominated flame retardants. We unexpectedly found very high levels of PCBs in two homes with no obvious source; one home's resident had higher blood levels than anyone in the CDC National Exposure Report. We discovered the likely cause was a common floor finish used in the 1950s and 1960s.[18] This story is not simply the legacy of a bygone era. In our latest research, we found levels of brominated flame retardants in California blood samples and household air at 2 to 10 times the levels elsewhere, likely due to the state's unique furniture flammability standard, which encourages use of these chemicals.[19] These findings are the result of our unfortunate "innocent until proven guilty" approach to placing chemicals into widespread use.

Very few of the chemicals identified as animal mammary gland carcinogens or EDCs have ever been included in a human breast cancer study. Studies that *have* been done are often limited by lack of good measures of exposure. Nevertheless, the epidemiologic literature provides some evidence of associations between chemical exposures and breast cancer. Four studies of PCBs show higher breast cancer risk in women with a genetic variation that affects its metabolism. A unique study with access to stored blood collected in young women in 1959-1967 found 5-times higher breast cancer risk associated with higher DDT exposures before age 14.[20] Some studies of PAHs, air pollution indicators, environmental tobacco smoke, dioxin, and organic solvents provide evidence of increased risk, particularly in young women or with exposure at a young age.[21]

Research and public health implications

Our current cancer research and public health programs simply are not set up to identify and respond to potential cancer risks from numerous environmental pollutants and chemicals in commerce. I recommend to you the California Breast Cancer Research Program (CBCRP) Special Research Initiative[22] as an alternative model that begins to address the priorities for change that I outline below.

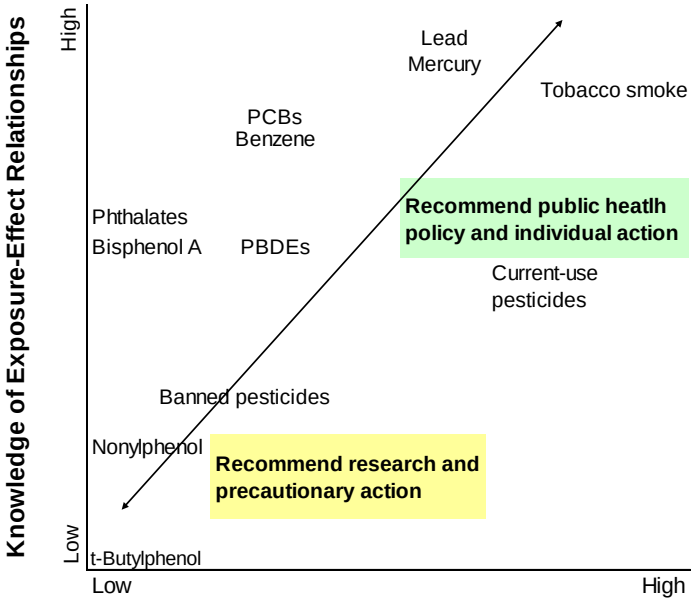
Tackle chemicals and pollution policy. Most importantly, we must define energy- and chemicals-production and use as cancer issues. Our nation's cancer program must concern itself with production and use of chemicals across our economy from the fuel efficiency of vehicles and energy production to the use of EDCs in toys, wrinkle-free clothing, food processing, and computers; and the protection of water supplies from human, animal, agricultural, and industrial wastes. America needs a systematic program that requires health assessment of synthetic chemicals – old and new -- as a prerequisite for

use. Europe, Canada, and California are developing or have already begun implementing models to draw upon for a US program.

Develop and apply methods for chemicals screening. As a basis for chemicals policies, we need to apply mutagenicity tests and other existing methods to identify carcinogens, EDCs, and developmental toxicants. We must also develop new methods, including high throughput tests to screen larger numbers of chemicals more thoroughly and at realistic cost. Pharmaceutical companies are using new technologies for drug discovery; we need public investments to apply these techniques to chemicals screening.

Develop and apply methods for exposure assessment. Similarly, we need new methods to measure exposure in environmental and biological samples and expanded laboratory capacity to evaluate samples from diverse communities and settings. New methods are needed to integrate effects of chemical mixtures. The National Exposure Report is an important monitoring tool that should be expanded to additional chemicals and more detailed subpopulation assessments, and we should immediately update the 1980 assessment of women's workplace chemical exposures.

Expand the universe of target chemicals. Current grants programs emphasize additional study of the chemicals we already know the most about (in the upper right quadrant of the graph below), rejecting higher-risk proposals to study exposure sources and health effects of chemicals with little prior evidence (lower left quadrant).



(adapted from Brody et al, 2007) [23]

Increase funding for agencies with environmental science expertise. Government programs with the expertise to advance environmental cancer research and risk reduction are the National Institute of Environmental Health Sciences, including the National Toxicology Program; the US Environmental Protection Agency; the National Center for Environmental Health at the US Centers for Disease Control and Prevention; the National Institute for Occupational Safety and Health; and the intramural Occupational and Environmental Epidemiology Branch of the National Cancer Institute. New funds should be directed through these centers.

Support public engagement. In order to guide public interest science and inspire public commitment to research and policy change, scientific leaders must take responsibility for forming research partnerships that engage, educate, and empower Americans to participate in environmental health science and policy

development. These efforts should achieve the same standards of excellence we expect of technical science. The NIEHS community based participatory research program and CBCRP offer useful models, and there is much room for expansion and further innovation.

Invest for the long-term in the best cohort studies. While my core message is to de-emphasize expectations for epidemiology in the short-term, well-designed cohort studies with excellent environmental exposure assessment will yield important knowledge in the long-term. The National Children's Study, Sister Study, Agricultural Health Study, Breast Cancer and the Environment Research Centers, and studies of accidentally exposed cohorts are examples of important resources for our future. If the costs seem daunting, consider the alternative cost of not pursuing prevention, including ballooning expenses for chemotherapies.

If we take steps to protect ourselves and our children from chemicals that cause cancer, we will also see benefits for numerous other health endpoints, including diabetes, obesity, neurological disease, and infertility. We will strengthen our economy by supporting green technologies.

Silent Spring Institute was founded as an independent research organization by leaders of the Massachusetts Breast Cancer Coalition to conduct environmental research with a goal of prevention. It was named, of course, in honor of Rachel Carson who herself died of breast cancer two years after publication of her world-changing book. She wrote, "For those in whom cancer is already a hidden or a visible presence, efforts to find cures must of course continue. But for those not yet touched by the disease and certainly for the generations as yet unborn, prevention is the imperative need."[24]

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