Cancer and the environment: Filling knowledge gaps together

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When considering disease etiology, we need to view the role of the environment along the continuum from health to disease for individuals because we know that there are complex interactions between genes, their molecular expression, and environmental factors over a person's lifetime. We clearly have huge gaps in our knowledge along this continuum, and these gaps are natural opportunities for research. There are many factors to consider as we assess the relationship between environmental exposures over a lifetime. One factor is persistence of chemicals that “live” beyond their initial intended use. Another factor is the fact that “inert ingredients” are not really inert. “Low dose” is also another consideration. We need to understand the biological effect of low dose exposure and we should clearly define what they mean by low dose research. For example, are we measuring the administered dose, or the internal/circulating dose? There are new types of toxicity as well. For example, endocrine disruptors and engineered nanomaterials are significant classes of materials deserving significant research. Timing of exposure is a significant feature in characterizing toxicity. Environmental exposures can have a greater impact in early or later life-stages. Finally, mixtures of chemicals are an important consideration. Humans are always exposed to multiple chemicals. In short, we must remember that there is no such thing as “not exposed.” Everyone has been exposed to many and various environmental agents.

Fig. 1 Dr Linda BIRNBAUM, Director, NIEHS & NTP, USA

Traditionally the biomedical and environmental health research communities have thought of disease etiology in two distinct ways — genes cause disease, or environmental exposures cause disease. In the gene-centric approach, a single mutation alters a single protein, which alters a single activity, causing a single disease. In the environment-centric approach, exposure to a single chemical alters a single gene or protein, which alters a single activity, causing a single disease.

Of course, we know that this is an extreme over-simplification. Even in cases of ‘genetic diseases’ such as cystic fibrosis, environmental exposures are known to exacerbate symptoms; and in an ‘environmental disease’ such as asbestosis, genetic susceptibility can influence disease susceptibility and severity. Therefore, we need to view the role of the environment along the continuum from health to disease for individuals because we know that there are complex interactions between genes, their molecular expression, and environmental factors over a person's lifetime.

Environmental factors and the disease continuum

If we can think of the progression of these complex, interrelated events, we can consider environmental and lifestyle factors as creating an exposure which results in an internal dose leading to early biological effects-altered structure or

function and ultimately, clinical disease. We clearly have huge gaps in our knowledge along this continuum, and these gaps are natural opportunities for research.

There are many factors to consider as we assess the relationship between environmental exposures over a lifetime.

Chemicals are persistent

One factor is persistence. Chemicals “live” beyond their initial intended use. Understanding the persistence of a chemical is a key criterion in toxicity testing. We should determine the persistence of a chemical before its widespread introduction and distribution into the environment. Also, if a chemical is ubiquitous, it may achieve “persistence” due to continuous exposure.

Ingredients are not inert

Another factor is the fact that “inert ingredients” are not really inert. For example, pesticide products contain both “active” and “inert” ingredients, both of which are key to the effectiveness of the pesticide. And yet, laws do not require the inert ingredients to be identified by name or percentage on the label. The public may assume that inert ingredients are non-toxic, but in fact, many are simply not tested for toxicity.

How do you define “low dose”?

“Low dose” is also another consideration. It is now known that different doses of a chemical result in different biological effects. Tests of effects at high dose are no longer adequate to determine the full spectrum of effects from a given chemical. We also need understand the biological effect of low dose exposure, and we should clearly define what they mean by low dose research. For example, are we measuring the administered dose, or the internal/circulating dose?

New toxicity

In addition to these factors, there are new types of toxicity as well. Endocrine disruptors are exogenous agents that interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes. Engineered nanomaterials are three dimensional particulates with one dimension less than 100 nm and possessing novel optical, magnetic, or electrical properties that emerge at the nanoscale and have unknown biological consequence. Each of these is a significant class of materials deserving significant research.

Exposure during development

Timing of exposure is a significant feature in characterizing toxicity. People vary in their susceptibility to chemical exposures, and these exposures can have a greater impact in early or later life-stages, and in those with pre-existing conditions or genetic-based vulnerabilities. Development is a highly integrated process, and the effect of exposure at the early stage of life and the long-term consequences cannot be underestimated.

Chemical mixtures in everyone

Finally, mixtures of chemicals are an important consideration because the whole may be greater than sum of the parts. Humans are always exposed to multiple chemicals. It is difficult to decipher how exposure to many chemicals will influence the effects of each one – both in time and space. In short, we must remember that there is no such thing as “not exposed.” Everyone has been exposed to many and various environmental agents.

Given these special considerations, we should ask, “What kinds of research programs are best suited to answer the modern questions of toxicology and environmental health?” Following are some National Institute of Environmental Health Sciences (NIEHS) research initiatives designed to explore these complex interactions with state-of-the-art research techniques:

Genetics, Genomics and Bioinformatics for Pathways Research

Using already existing public databases that provide associations between alterations in gene structure and function with human diseases, a team of NIEHS scientists is using this information to establish disease and toxicity pathways. The intersections of toxicity pathways and disease pathways and human diseases can be visualized in cluster networks.

The Genes, Environment, and Health Initiative

This is an ongoing 5-year initiative to understand the interactions of genetics and the environment with respect to influences on asthma, diabetes, cancer and other common illnesses. The initiative is supporting the development of new procedures for analyzing genetic variation in groups of patients with specific illnesses, along with new technologies for measuring exposures to chemical and biological agents, dietary intakes, physical activity, psychosocial stress and addictive substances. Through our research grants program, we are involved in developing an array of tools to more precisely measure, on an individual level, the myriad of environmental agents and situations we encounter in daily life.

Breast Cancer and the Environment Program

The Breast Cancer and the Environment Program is an ongoing collaboration between the NIEHS, the National Cancer Institute (NCI), and private partners providing \$35 M over a seven year period for cooperative epidemiologic, basic biology, and outreach activities. This has been an inclusive collaborative study — at all levels — of basic scientists, epidemiologists, outreach experts, and community advocates. A 5-year renewal of this program is in development and is projected to expand upon the early findings into various windows of susceptibility that will encourage new directions on the role of common environmental exposures on breast cancer risk. The program is planned to provide approximately an additional \$37 M over the project period to attract new expertise and concepts.

The Agricultural Health Study

A cooperative program between NIEHS, and other U.S. agencies such as the NCI, the Environmental Protection Agency and the National Institute for Occupational Safety and Health to prospectively study farmers, their spouses and children is determining the factors contributing to an increased risk of cancer among farmers. Farmers are a unique occupational group because they are exposed to many potentially hazardous pesticides and other chemicals. The opportunity to study spouses and children of farmers made the collaboration with the NCI especially attractive.

The Sister Study

This prospective cohort study recruited nearly 51 000 women aged 35–74 with a sister with breast cancer. While genes are important in breast cancer risk, breast cancer genes have only been identified in less than 10% of cases. The concordance rate for monozygotic twins is 14%–20%, and known risk factors explain less than 50% of breast cancer variation. Early results from the Sister Study show an increased risk of uterine fibroids associated with their mother's diabetes or use of diethylstilbestrol (DES), being fed soy formula, and lower childhood socioeconomic status (SES).

Even with these NIEHS initiatives, the environmental health research enterprise clearly needs to invest in several areas:

- Expanded understanding of environment, timing of exposure, and lifestyle factors in individual susceptibility to disease
- Improved measurement of exposure and body burden
- Biomarkers of exposure, disease progression, and therapeutic efficacy
- More precise linkage of environmental factors to biological effects
- Enhanced understanding of disease mechanisms
- Identification of therapeutic targets

I am confident that with the right investments, environmental health research can provide critical insights into complex diseases and substantially advance our ability to provide effective preventive measures and treatments.