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NIH National Institute of Environmental Health Sciences

Breast Cancer and the Environment: Controversial and Emerging Exposures

Virtual Workshop Summary

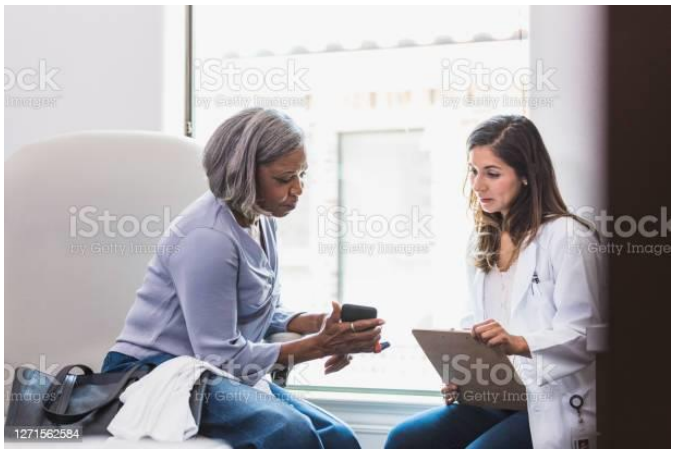
Friday, May 14, 2021

U.S. Department of Health & Human Services | National Institutes of Health

Introduction

The relationship between environmental exposures and cancer risk is a topic of compelling interest because of the widespread and varied exposure to carcinogens and endocrine disrupting compounds (EDCs) in the environment. The impact on breast cancer risk is of particular importance considering the hundreds of thousands of women and their families in the United States every year affected by the most common cancer in women.

To provide effective, evidence-based public health decisions to reduce exposures and cancer risk in the population requires large investments and coordination between those making etiologic observations and those assessing the risk from exposure and its consequences on women's health. Further investigation of the etiologic role of exposure to environmental contaminants and its public health impact remains an important priority. Rapidly evolving science, including advances in highly sensitive tools to detect very small amounts of environmental contaminants or subtle but relevant biological effects, epidemiological and analytical methods, and mutational signatures in tumors, are presenting exciting research opportunities. Therefore, there is a need for more efficient deployment of current approaches and new thinking on how we study this topic and how we convey risk and related information for public health decision-making.



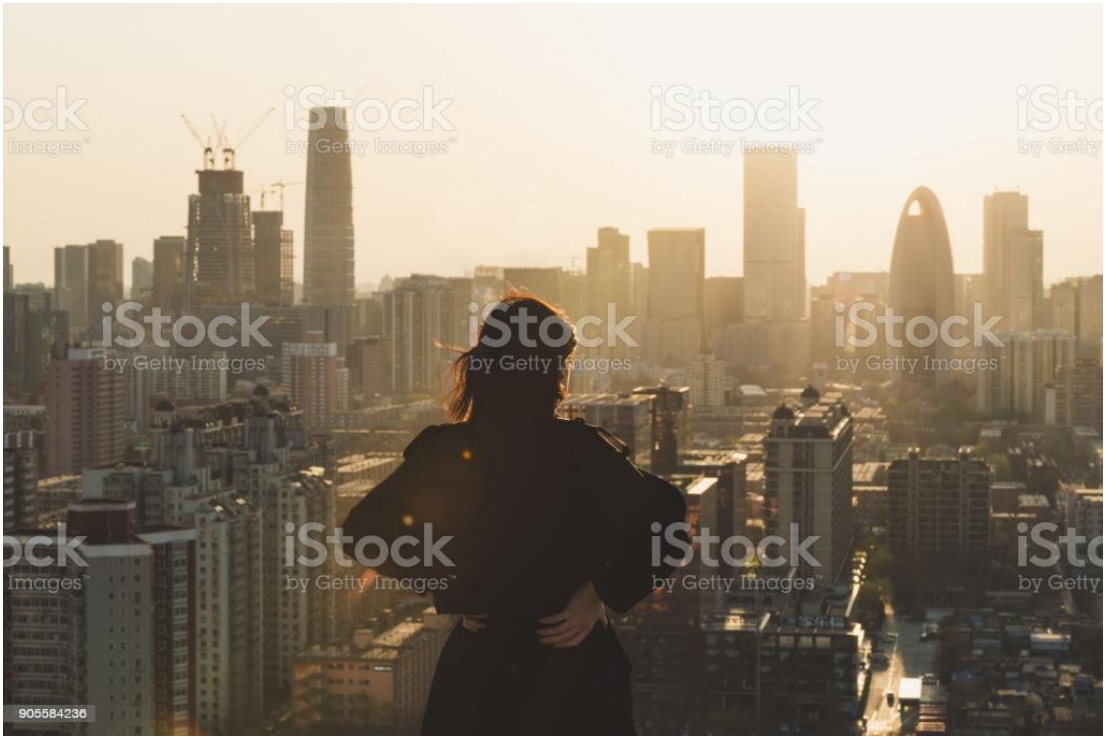
The National Cancer Institute (NCI) and National Institute of Environmental Health Sciences (NIEHS) have a long history of collaboration on breast cancer initiatives, including the Breast Cancer and the Environment Research Program (BCERP), a multidisciplinary effort on the impact of the environment on breast development and cancer risk, the Long Island Breast Cancer Study Project, and other studies of breast cancer risk. The NIEHS intramural program's Sister Study cohort, established to identify environmental and genetic risk factors for breast cancer, has fostered both intramural and extramural research collaborations. The results of these and other studies should form the foundation for other parts of the federal government to assess chemicals with the potential for mammary gland carcinogenesis or disease risk modification, including the Food and Drug Administration (FDA), Environmental Protection Agency (EPA), Centers for Disease Control and Prevention (CDC), and National Toxicology Program (NTP). Continued research and public health efforts, in conjunction with the perspective of the breast cancer advocacy community and their contributions in disseminating findings, are

critical to making progress in the assessment of risks and on breast cancer prevention at the population and individual levels.

The wide international variation and temporal increases in breast cancer incidence illustrate the importance of lifestyle, contextual, and environmental factors. Studies have estimated that established risk factors for breast cancer could explain up to 70% of postmenopausal breast cancer cases in the US non-Hispanic White population. However, only approximately one-third of cases could be prevented by modifying lifestyle factors such as weight, menopausal hormone therapy, alcohol use, and physical activity, and in particular, little information is available for racial and ethnic minorities in the United States. Moreover, the estimates have yet to incorporate new lines of evidence, such as light at night, low-dose radiation, or chemical exposures.

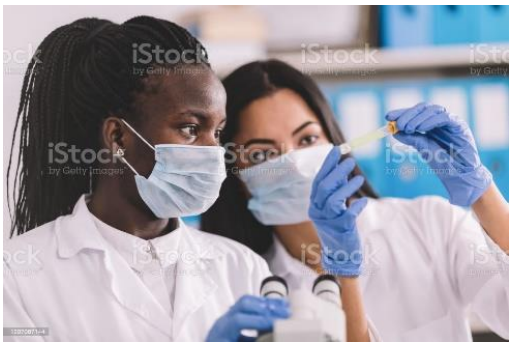
Thus, there is a clear need to better understand how these risk factors could have an impact on breast cancer risk and prevention, particularly in minority populations and low-income communities, who are disproportionately exposed to chemicals in the environment and typically underrepresented in research studies.

NCI and NIEHS organized the Breast Cancer and the Environment: Controversial and Emerging Exposures workshop to convene a group of expert researchers to provide updates on the "state of the science" for selected chemical and physical agents in the environment in relation to the risk of developing breast cancer. Participants were also asked to identify new research opportunities and approaches to address current gaps in knowledge.



Setting the Stage

According to work by the International Agency for Research on Cancer (IARC) Monographs over the last 50 years, there are five "known" breast carcinogens with "sufficient" evidence in humans (alcohol, diethylstilbestrol, estrogen–progestogen contraceptives, estrogen–progestogen menopausal therapy, and x-, γ- radiation), and seven "suspected" carcinogens with "limited" evidence in humans (dieldrin, ethylene oxide, polychlorinated biphenyls, night shift work, estrogen menopausal therapy, digoxin, and tobacco smoking).



Identifying carcinogenic hazards relies on evidence from studies in animals and human populations, and human evidence often comes from populations occupationally exposed to high levels of chemicals. Because women are not often represented in typical occupational settings, this presents challenges for identifying cancer risks in women. Animal studies have identified many chemicals with sufficient evidence as mammary carcinogens or with potential to increase breast cancer risk through endocrine-disrupting properties, but few of these chemicals have been studied in humans. Some of these chemicals have also been shown to influence important risk factors for breast cancer such as obesity and age at menarche.

However, despite decades of research using multiple approaches to identify environmental carcinogens in humans, the aggregate evidence is limited. Current approaches have only identified a very small number of clear-cut breast carcinogens in humans. Although the concordance between animal and human studies for known or suspected human carcinogens has been weak, there remain important concerns about a much larger number (100s or 1000s) of agents yet to be studied in humans. Of all known mammary carcinogens with sufficient evidence in animals, only one (estrogen–progestogen menopausal therapy) has sufficient evidence of breast carcinogenicity in humans and one (estrogen menopausal therapy) has limited evidence. The weaker or lack of evidence for other compounds could be due to the small sample sizes in many occupational or highly exposed environmental epidemiology studies in women, which have limited the evaluation of candidate chemical exposures. Using mechanistic endpoints (biological consequences of exposure rather than cancer endpoints) in exposed women could accelerate breast carcinogen identification.

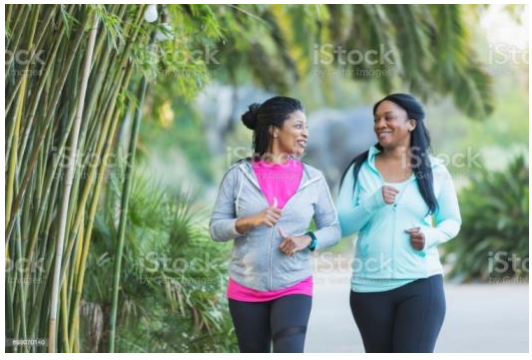
Both animal and human studies have shown that breast tissue changes in form and function over the life course and that there are windows of susceptibility *in utero*, in early life, during puberty, and during pregnancy when the tissue may be most vulnerable to chemical exposures; changes initiated during these windows of susceptibility can persist or worsen

later in life. Early indications are that risk associations with environmental factors could be identified in populations highly susceptible to breast cancer (e.g., women with a positive family history or with known genetic susceptibility) or by focusing on breast cancers occurring in younger women or in those populations knowingly exposed to chemicals during windows of susceptibility (early life, puberty, pregnancy). Difficulties in conducting studies that capture relevant windows of susceptibility could contribute to the challenges in establishing cancer risks in women.

Notably, breast cancer is not a single disease but a group of disease subtypes with different etiologies and prognoses, and some subtypes disproportionally affect certain populations. In particular, African-American women are diagnosed with more aggressive cancer subtypes at a much earlier age and later stage, heightening the risk for poorer outcomes. Another consideration is that the burden of environmental exposures and related illnesses is greater in minority and low-income communities, reflecting consequences of structural racism. Thus, future research in environmental risk factors for breast cancer must consider etiologic heterogeneity, health disparities, and environmental justice.

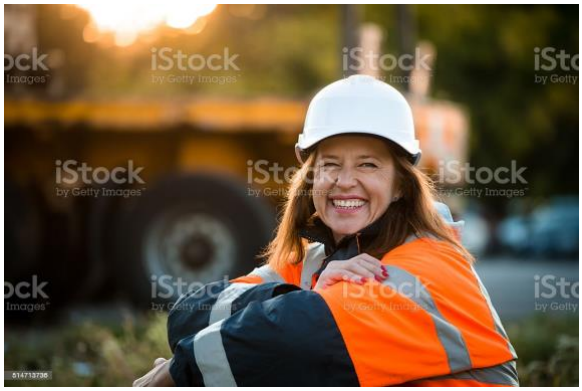
SETTING THE STAGE: KEY POINTS

- Integration of information from animal and human studies is needed to identify environmental contaminant hazards. Novel study designs in women are critical to evaluate the concordance between sources of evidence.
- Consideration of windows of susceptibility, susceptible populations, mechanistic endpoints in highly exposed populations, and etiologic heterogeneity by subtypes should increase consistency of signals and the chances of establishing breast toxicants in human populations.
- Studying diverse populations, particularly women from racial/ethnic minorities and underserved populations, is critical to understanding the impact of the environment on breast cancer risk and to inform strategies for prevention.



Chemical and Physical Factors

This section evaluates the state of the science of selected chemical/physical factors and breast cancer risk considered during the workshop, including exposures to radiation, light at night, hazardous air pollutants (HAPs), contaminants in drinking water, and the potential impact of climate change. While not an exhaustive list, these exposures provide insights into the methodological and analytical issues required to tackle the effects of these and other exposures not well characterized in humans. Topics covered range from well-established risk factors to exposures of current concern for which the literature is mixed.



Ionizing radiation is a well-established cause of breast cancer and its effects are greatest when exposure occurs early in life. Other risk factors (e.g., reproductive history or genetic makeup) could influence susceptibility to radiation-induced breast cancer. Studies have shown that even low-dose exposure to ionizing radiation such as that used in CT scans and mammograms can cause breast cancer, with similar risks for estrogen receptor (ER)–positive and ER-negative cancers. Low-dose medical radiation is likely to explain about 1% of annual breast cancer diagnoses in the United States. Although most of these procedures have valid medical indications, the appropriateness and lowest effective dose of CT scans should be determined to avoid unnecessary exposure. This is particularly important in the United States, which performs the most scans in the world, nearly three times more than in the United Kingdom.

Light at night exposure can come from factors like shift work, ambient lighting, use of electronic devices, or traveling across time zones that leads to circadian disruption. According to IARC, shift work is a suspected carcinogen with "sufficient" evidence in experimental animals and systems but "limited" evidence for breast, prostate, and colorectal cancers in humans. However, the NTP recently has concluded that there is high confidence for a causal relationship between persistent night shift work and human cancer (approximately two-fold elevated breast cancer risk in premenopausal women) and moderate confidence for light at night or insufficient daylight exposures.

To close gaps in research, there is a need for better exposure assessment, including metrics of shift work (e.g., rotating versus permanent shift work) or indoor light at night, increased spatial resolution of satellite imagery to measure amount and type of outdoor light at night, accounting for human behaviors that mitigate or enhance human interaction with outdoor light at night, and distinguishing between light exposures at different wavelengths. Additional work is needed to determine if light at night is a proxy for other factors related to

urban living or sleep disruption, how it could act in combination with shift work, and what the possible mechanisms of action (biological mediators such as circadian disruption) and relevant windows of susceptibility are. Biological measures of circadian disruption could also help in establishing risk associations and understanding biological mechanisms.

Animal studies have demonstrated that many chemical contaminants found in air, water, and dietary sources are mammary carcinogens and developmental/functional toxicants, but many have not been confirmed by epidemiological studies in women. HAPs are known or suspected to cause cancer or other serious diseases; they are captured and modeled by the EPA National Air Toxics Assessment (NATA) but have no ambient air quality standards. HAPs include mammary carcinogens and endocrine disruptors that have been studied in relation to breast cancer risk in a few large cohorts of women in the United States followed for many years for cancer outcomes. Exposure assessment is based on geographical NATA monitoring data because of the difficulties in measuring personal exposures in large epidemiological cohorts. These studies found provocative risk associations with HAPs, some present only for ER-positive or ER-negative tumors, or within subgroups of the population. There are consistent findings between human and animal studies, particularly for metals (arsenic, cadmium, lead, and mercury).

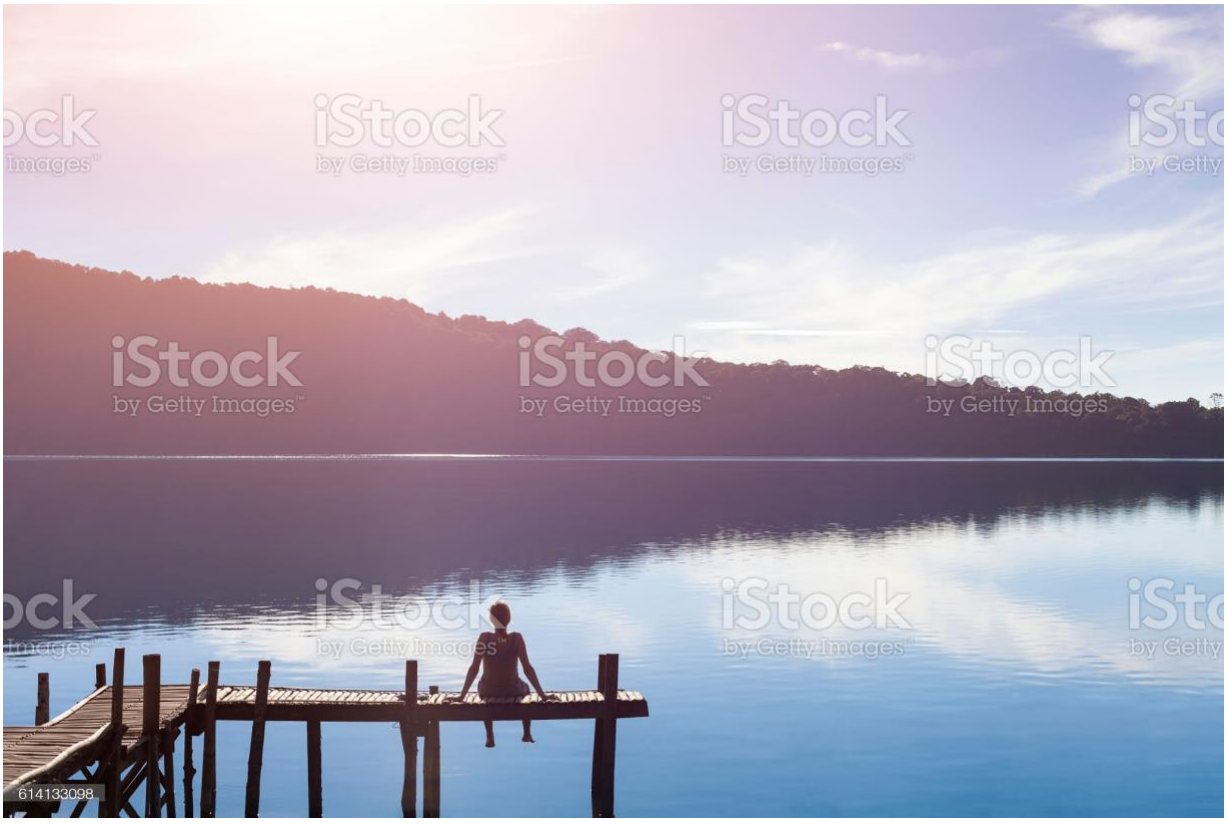
The potential impact of HAPs on breast cancer risk warrants further investigation in large and longitudinal studies with multidisciplinary perspectives on measuring personal exposures to low levels of complex chemical mixtures (e.g., through highly sensitive monitors and biomarkers), consideration of windows of susceptibility, susceptible and underserved populations, new analytics to address the complexity of data, and improved nationwide monitoring data on pollutants.

EPA and numerous states have set health advisory and/or regulatory levels for about 80 contaminants in drinking water, including disinfection byproducts (DBPs), pesticides, nitrate/nitrite, lead, arsenic, and persistent endocrine disruptive chemicals (pesticides, polychlorinated biphenyls [PBCs], polyaromatic hydrocarbons [PAHs], per- and polyfluoroalkyl substances [PFAS], and dioxins). Epidemiological studies commonly leverage state and national monitoring data on these chemicals to study relationships with cancer, finding some associations with risk but no consistent evidence for breast cancer based on a limited number of studies. Some persistent endocrine disruptive chemicals like pesticides (i.e., dichlorodiphenyltrichloroethane [DDT] and dichlorodiphenyldichloroethylene [DDE] in particular) and dioxin have been associated with breast cancer risk; however, drinking water is not considered to be their primary route of exposure.

With respect to contaminants in diet, there is some evidence from epidemiological studies for risk associations and it is difficult to disentangle adverse effects of dietary contaminants from the beneficial effects of specific components of diet (e.g., fruits and vegetables) or dietary patterns. There is limited evidence for increased breast cancer risk from exposure to

carcinogens produced from high-temperature cooking methods (PAHs, heterocyclic amines) as well as for nitrate/nitrite preservatives in processed meat. Industrial sources of dioxins and PBCs have been associated with elevated breast cancer risk in highly exposed populations in occupational settings or from accidental environmental releases to air. Environmental accidents may lead to contamination of food products; however, the contribution from diet sources in normal settings is harder to assess. There are mixed signals for bisphenol A (BPAs) and phthalates contaminants from food packaging, and for PFAS also found in food packaging and water.

Of particular interest for further study are legacy and emerging unregulated contaminants such as PFAS that are ubiquitous in the population and persist in the environment for many years, and 3-chloro-4-dichloromethyl-5-hydroxy-2(5H)-furanone (MX), a highly mutagenic chlorinated byproduct found in water that has not been studied in relation to breast cancer. Studying chemical and physical factors from modifiable sources is particularly important since once we know that something in that source is harmful, it can lead to changes in behavior (e.g., eat a different food or use an alternative water source) or regulations to remove or decrease the exposure source.



A major challenge in studying chemical contaminants in air, water, and dietary sources is the ability to obtain measurements during relevant periods of exposure, particularly for compounds that are rapidly metabolized, since this requires serial measurements over an extended duration in sufficiently powered studies to observe a robust signal.

Epidemiological studies often use reconstruction of past exposures based on questionnaires or historical monitoring data linked to residential or occupational histories. However, this relies on recollection of past events or on availability of state or national monitoring data that is lacking for many contaminants, or, when available, is often sparse and potentially not representative. Promising approaches include investing in expanding and improving monitoring data on contaminants, setting up large, long-term epidemiological studies with serial measurements, developing highly sensitive technologies to measure low levels of exposure and intermediate endpoints, and developing new biomarkers of exposures and biological effects. As these exposures often co-occur, methods quantifying numerous suspect compounds simultaneously in one sample could greatly accelerate exposure identification.

In addition, work is needed to address the direct and indirect impact of climate change on breast cancer outcomes, including chemical exposures due to water depletion, changes in temperature and humidity, frequency/intensity of severe weather events (e.g., hurricanes, flooding), and eutrophication of surface waters (e.g., development of harmful algal blooms). Natural disasters could also affect other determinants of breast cancer diagnosis and survival, such as access to care and screening, and can impact stress.

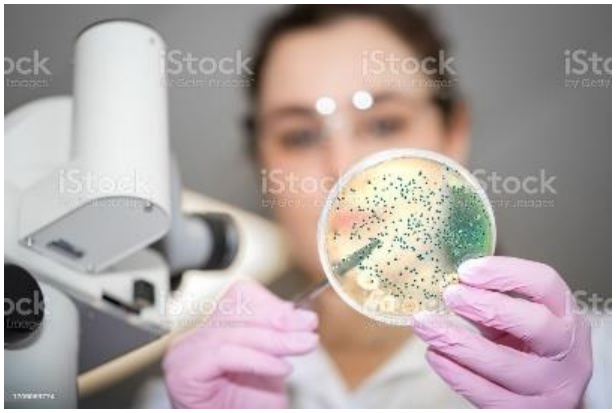
Long-term prospective cohort studies collecting exposure information and biological specimens from study participants prior to cancer development, such as those participating in the NCI Cohort Consortium are very valuable resources to study the impact of the environment on breast cancer development. The NCI Connect for Cancer Prevention Study is a new prospective cohort of 200,000 adults free of cancer at enrollment that provides an opportunity to address some of the gaps in knowledge in this area through detailed and repeated exposure assessments prior to breast cancer diagnosis incorporating residential and occupational lifetime histories, water sources, diet, drinking water intake, wearable monitors, and serial biological specimens for biomarker studies. This and other new cohort studies such as the NIH All of Us Research Program following participants from more recent birth cohorts will have the advantage of availability of geographic information systems (GIS)–linked exposure data during relevant exposure periods.

CHEMICAL AND PHYSICAL FACTORS: KEY POINTS

- There are substantial challenges to studies of environmental factors and breast cancer, including the nature of environmental exposures (e.g., low level and widespread, variability over time and intermittency, rarely occurring in isolation). Occupational studies, often a first opportunity to evaluate specific chemicals that also occur in the general environment at lower doses, are limited by the relatively smaller number of women in occupational settings.
- Improved assessment of environmental exposures requiring new tools and infrastructure is critical to making progress. This includes questionnaires, wearable devices, accurate and affordable assays, and collaborations with the agencies that collect monitoring data to ensure suitability for research.
- Research should address contextual factors such as neighborhood environments, socioeconomic status, and race/ethnicity.
- Novel study designs, statistical approaches for big data and integrative analyses, and laboratory techniques and tools are emerging and should enable novel integrative approaches.
- The magnitude of associations is likely to be small but of public health importance because of widespread exposures in the population. Measures of public health impact are needed to inform policies and potential interventions to mitigate risks.

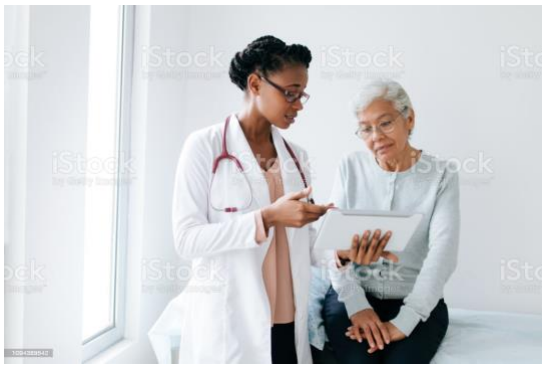
Biomarkers

Physical–chemical compounds are among many external factors across the lifespan that can influence the risk of developing breast cancer and other diseases; notable are changes in ecosystems, lifestyle, and social factors, which until recently were hard to capture. The "external exposome" is hypothesized to influence biological systems (that can be thought as the "internal exposome", e.g., epigenome, transcriptome, proteome, metabolome, and microbiome), in combination with the inherited genome, to cause disease. Biomarkers measured in biological specimens (e.g., blood, saliva, urine, stool) using novel "-omic" technologies can characterize the whole or large parts of the genome and exposome, providing unprecedented opportunities to take a comprehensive look at the impact of the environment on biologic systems and health. Genome-wide association studies (GWAS) using genetic scans have identified hundreds of variants related to breast cancer susceptibility. Individually these variants are associated with small differences in cancer risk, but their combination using polygenic risk scores has proven to be more informative.



Studying the ever-changing exposome is even more daunting, yet new developments are emerging that show promise for identifying novel exposures and studying the impact of combinations of exposures on breast cancer risk. People are exposed to thousands of chemicals in the environment, most of which have never been tested adequately for safety. Thus, there is a need for broad explorations of different chemicals that could affect health outcomes. Targeted and nontargeted high-resolution mass spectrometry has greatly increased the ability to identify and quantify endogenous compounds such as nutrients, contaminants, metabolites, and chemical pollutants in biological samples. That technology has enabled research to combine data from exposure scans that measure the internal dose of more than 1,000 chemicals with metabolite scans that capture a wide range of biological systems simultaneously. These exposome scans are providing important insights into the toxicity of chemical mixtures in humans. While their use in breast cancer studies is still at an early stage, there are some promising findings showing increases in circulating metabolites related to multiple factors that can influence breast cancer risk, including cell proliferation, systemic inflammation, alcohol use, and insulin resistance. Because of the expected low levels of exposure to numerous compounds with weak risk associations, exposomics studies will require highly sensitive assays in very large samples (perhaps in the millions), with resultant challenges in data analytics to integrate and interpret large amounts of data from multiple platforms in meaningful ways.

The epigenome, in particular methylation changes in the DNA, has been proposed as a biosensor of past or cumulative exposures, or a disease mediator. However, scans of the methylome using epigenome-wide association studies (EWAS) or studies of specific methylation changes and breast cancer risk have yielded mixed results. The lack of clear and consistent signals could be due to using blood-based methylation as a surrogate for target (breast) tissue (although there is increasing evidence of concordance between changes in blood and target tissues), insufficiently powered studies to detect weak signals, differences in timing of blood collection relative to cancer onset, and/or study biases. Further research with improved designs and measures of the epigenome are needed to characterize the relationships between specific exposures at different windows of susceptibility and methylation (or other epigenetic) changes in different target tissues, to determine their role as possible mediators or modifiers of the effects of the environment on breast cancer risk, and to assess the impact of risk-reducing interventions such as weight loss or metformin use. This will require collaboration of experimental and epidemiological scientists.



Characterizing the microbiomes of the gut and breast could lead to the discovery of modifiable intermediates connecting environmental chemicals and breast cancer. There is some evidence that the mammary microbiota differs between cancerous tissue and adjacent healthy tissue and that the gut microbiota can influence breast cancer prognosis, response to therapy, and estrogen metabolism. But the relation of the gut and breast microbiota with breast cancer development is largely unknown. Progress in this area will require frequent and repeated collection of stool or healthy breast tissue through biopsies or cells in breast milk or nipple aspirate in large prospective cohorts, with careful collection methodologies to rule out artifactual associations driven by contamination. It may be possible to conduct human knockout studies using antibiotics to clarify the importance of the human gut microbiome. These studies need to consider windows of susceptibility to ensure they capture important associations, including early in life when the gut microbiome is first established. In addition, feeding studies would be useful in understanding the effect of food contaminants, including those from packaging that exist in the general population diet. Dietary intervention studies using pre- and probiotics should also be considered.

There is considerable enthusiasm for "multiomic" analytical approaches to characterize the exposome and study its relationships with breast and other cancers. Large-scale, prospective cohort studies in diverse populations with serial collections of data and biospecimens to measure changes over time prior to diagnosis and capture windows of susceptibility, such as in the new NCI Connect for Cancer Prevention cohort, will be

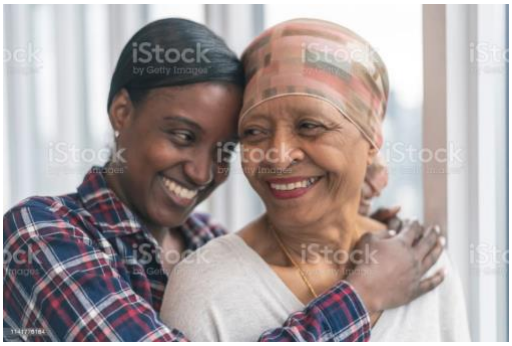
instrumental. This cohort will also collect premalignant tissue and cancer tissue after diagnosis to study biomarkers of carcinogenic transformation and etiologic heterogeneity. Using intermediate endpoints such as mammary gland density could also help establish associations between the environment and breast cancer. Another promising area is the study of somatic mutational signatures in tumors to trace back exogenous exposures and endogenous processes related to the origins of cancer.

BIOMARKERS: KEY POINTS

- Tremendous scientific opportunities are afforded by advances in -omic technologies to characterize the external and internal exposome to shed light on the complexity of associations between the environment and breast cancer, and to establish effective prevention programs.
- Collection of serial, prediagnostic biological specimens in large-scale, rigorous epidemiological cohorts and in experimental studies, and development of highly sensitive and affordable -omic technologies are needed to make progress.
- Comprehensive assessments of the exposome are in early phases and limited in size. Studies to date have identified associations with potential breast cancer risk factors rather than breast cancer itself.
- A combination of experimental and epidemiological data can help interpretation and understanding of biological mechanisms.
- Increasing synergy among ongoing and planned biomarker studies and new approaches in big data analytics for high-dimensional data will be needed to fully realize the potential of these approaches.

Concluding Remarks

There are pressing concerns about the role of widespread environmental exposures in breast cancer risk. Many potentially toxic chemicals are ubiquitous in the ambient environment, in consumer products, and in diet and drinking water. Despite improvements in breast cancer treatments and case fatality, breast cancer remains the most common cancer among women and a leading cause of cancer death. Recent evidence points to increasing racial/ethnic disparities in breast cancer mortality over time, making it crucial to pinpoint factors associated with increasing breast cancer risk and breast cancer disparities. However, despite extensive research on breast cancer and the environment over the years, with a few exceptions, we have yet to identify strong evidence for risk associations with specific exposures. Therefore, NCI and NIEHS have an obligation to contribute to the body of knowledge to help regulatory agencies make decisions about the public health risks of specific toxic agents. This is particularly important because even small increases in risk could account for substantial numbers of cancers when the exposures are widespread in the environment, particularly for the most common cancer in women in the United States.



While there are many opportunities for research, they are not without challenges. New thinking and approaches are needed to meet this public health obligation. For instance, existing research findings suggest the importance of focusing on specific windows of susceptibility, considering the role of multiple exposures and changes in exposures over time. The research also suggests the need for improved exposure assessment and identification of early biomarkers of breast cancer risk. Thus, the development of a detailed and feasible approach to investigating environmental agents that considers the many complexities and challenges of this type of research will be required to make progress. Addressing these complex issues is not only the responsibility of NCI and NIEHS but a broader problem that must be addressed by the wider scientific, advocacy, and regulatory communities. This will require cooperation and coordination to address the many research challenges using new and established approaches to better inform the public and serve as the basis for federal agencies to act upon. It will be critical to engage other institutions, such as the National Academy of Sciences, FDA, or other government agencies to continue to advance the development of metrics and frameworks for assessing the potential of environmental chemicals to directly contribute to breast cancer risk and the subsequent steps required to make important evidence-based public health recommendations.

Agenda

Co-chairs: M. García-Closas and D. Sandler

INTRODUCTION

Speakers: N. Sharpless, G. Collman, M. García-Closas

SESSION 1:
Setting the Stage

Windows of Susceptibility
Speaker: M.B. Terry

Integrating Human and Animal Evidence
Speaker: S. Fenton

Etiologic Heterogeneity/Tumor Subtypes/Signatures
Speaker: M. Troester

Contribution to Health Disparities
Speaker: L. Adams-Campbell

Comments
Moderator: A. Trentham-Dietz

Open Discussion
Discussants: L. McCullough, M. Schubauer-Berigan

SESSION 2:
Chemical and Physical Factors

Hazardous Air Pollutants
Speaker: P. Reynolds

Contaminants in Drinking Water and Dietary Sources, Climate Change
Speaker: R. Jones

Low-Dose Radiation
Speaker: A. Berrington de González

Light-at-Night
Speaker: F. Laden

Comments
Moderator: D. Sandler

Open Discussion
Discussants: A. White, M. Ward

SESSION 3:
Biomarkers

Exposomics
Speaker: R. Vermeulen

Epigenetics
Speaker: Z. Herceg

Microbiome
Speaker: K. Michels

Comments
Moderator: G. Gierach

Open Discussion
Discussants: M. Gaudet, P. Castle

GENERAL DISCUSSION

Speaker: D. Sandler

WRAP-UP AND NEXT STEPS

Speakers: N. Sharpless, M. García-Closas

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*Unable to attend.

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