Epidemiologic Contribution to Understanding the Environmental Impact on Women’s Health

*The NIEHS Sister Study*

Dale P. Sandler
Epidemiology Branch
National Institute of Environmental Health Sciences, NIH

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The Sister Study’s Contribution to Understanding the impact of Environmental Exposures on Women’s Health

Presentation overview

– Background on Sister Study cohort development
– Describe the resource and potential to address environmental health concerns
– Share examples of recent findings
– Consider opportunities and challenges
Why The Sister Study?

Concerns about rising breast cancer incidence led to concerns about risk associated with increasing chemical exposures

- Advocacy groups called for more studies
- Existing breast cancer studies focused on lifestyle, hormones, reproduction

ER-positive breast cancer decreased after WHI report on HRT, but incidence still high and rising for some groups

Breast cancer remains the leading type of incident cancer

- 281,550 new cases in 2021; 30% of all incident cancers in females

American Cancer Society 2021
Research on Environment and Breast Cancer Still Urgent

In 2012 & 2013, commissioned reports called for more environmental research
- Multi-disciplinary
- Consider genomics and gene x environment interactions
- Life-course approach

Sister Study well positioned to meet this need and consider newer approaches
- Chemical mixtures
- Exposome

Concerns about health impacts of climate change
- New technologies, exposure measures
- New urgency

IOM 2012, IBCERCC 2013
The Sister Study Design

Goal: enroll 50,000 volunteer women with a sister with breast cancer to address concerns about environmental exposures

- Sisters have 2-fold risk and higher prevalence of relevant genes or exposures
- Increased power to detect associations
- Sisters highly motivated and response rates high

Prospective design

- Addresses limitations of prior case-control studies
- Opportunity to study range of health outcomes
- Survival and health outcomes

Sandler et al., EHP 2017
The Sister Study – Overview of Data Collection

4,427 incident breast cancer cases through Oct.12, 2020
  – Allows study of subtypes and population subgroups

Sandler et al., EHP 2017

The Sister Study: Home (nih.gov)
Who We Enrolled

Goal to enroll diverse cohort – geography, age, race, ethnicity, exposures
  - Participants from all 50 states and Puerto Rico

Despite targeted outreach and restricted recruitment, cohort less diverse than U.S.

- 83% self-reported non-Hispanic White race/ethnicity (9% non-Hispanic Black, 5% Hispanic/Latina, 3% other)
- 51% completed college
- Average per-person household income $43,000 (vs. NHANES $23,000)
- 37% report excellent health (vs. NHANES 17%)

Passive follow-up of ~3,000 women who didn’t fully complete enrollment

Sandler et al., EHP 2017
Breast Cancer Windows of Susceptibility

Follow-up Questionnaires
Reproduction, Hormones, Health, Exposures, Stress, Quality of Life

Ages 35-74
Enrollment Questionnaires
Health and Exposures, Reproduction, Diet, Family History

Adapted from Martinson et al., 2013
Sources of Environmental Data

- Questionnaires – current and retrospective exposures
- Biological samples
- Household dust
- Geographic Information System (GIS) data
- Environmental exposure monitoring
- Personal monitoring (wearables)
Epigenetics and ‘Omics for Exposure Assessment

Internal Exposome
Metabolomics and exposomics
- Targeted and untargeted assays
- Identify new exposures and pathways

Epigenetics
Epigenetic mechanisms affected by
- Early development and aging
- Environmental and lifestyle exposures

CpGs and methylation-based markers of age acceleration linked to environmental exposures

➤ Methylation exposure signatures (e.g., smoking)
Sister Study Research

Wide-ranging topics and approaches

Chronic Disease Group & EB
- Risk factors for breast and other cancers
- Other outcomes
- Genomics (epigenetics)
- Early life/lifecourse
- Novel exposures (e.g., trauma, sleep)

Consortia
- Gene discovery and risk prediction
- Risk factors for cancer

Work with NIH and extramural colleagues, students

>270 papers since 2009; 17 extramural grants
Childhood Exposure to Vehicular Traffic and Breast Cancer Risk

Air pollution data limited before 1990
  – Wide range of birth years in cohort
Evaluated risk using self-reported data on roads and traffic at longest childhood residence

- Breast cancer associated with living on/near road with heavy traffic

*Referent – live more than 100 feet from road with multiple lanes or traffic barriers
Early Life Exposures and Breast Cancer Risk

Physiological Activity Ages 5-19 and Breast Cancer Risk

- Physical Activity Ages 5-19 and Breast Cancer Risk
  - Hazard Ratio
  - Physical Activity - hours per week
  - HHS Guidelines – 7+ hours week

Niehoff et al., Br Cancer Res & Treatment 2017

Environmental Tobacco Smoke and Breast Cancer

- Environmental Tobacco Smoke and Breast Cancer
  - Hazard Ratio
  - Years of Childhood ETS
  - In Utero (any HH)

White et al., Cancer Causes Control 2017
High Early Life Trauma Associated with Decreased Breast Cancer Risk, but Sexual Trauma May be Associated with Increased Risk

Association with sexual trauma modified by social support in childhood
- HR 1.23 (1.01, 1.50) without support
- HR 1.01 (0.82, 1.24) with support

Woo et al., Epidemiology 2022
Hair Products and Breast Cancer Risk

**Personal Care Products Questionnaire**
- Use at ages 10-13; 12-months prior to enrollment

Frequent use of hair straighteners in **adolescence** associated with 2-fold higher risk of **premenopausal** breast cancer.

Frequent use in **year before enrollment** associated with 50% increase in **postmenopausal** risk
  - Frequency of use greater for Black women, but associations similar

**Adult use** of permanent hair dye associated with 9% higher overall breast cancer risk; 45% higher for Black women

*White et al., Int J Cancer 2021; Eberle et al., Int J Cancer 2020*
Air Pollution and Breast Cancer

Exposures and effects may vary by region

NO₂ consistently associated with breast cancer risk but evidence for PM$_{2.5}$ mixed

Using air pollution monitoring data and land-use regression models, suggestive associations in Sister Study

Reding 2015: NO₂ associated with ER+ breast cancer

[RR 1.10 (95% CI 1.02, 1.19 per IQR)]; no association with PM$_{2.5}$

White 2019: NO₂ [HR 1.06 (95% CI, 1.02,1.11)] and

PM$_{2.5}$ [HR 1.04 (95% CI 0.98, 1.10)] associated with overall breast cancer

➢ Geographic heterogeneity in PM$_{2.5}$ chemical composition and exposure sources

Reding et al., CEBP 2015; White et al., EHP 2019
Healthy Diets and Breast Cancer Risk

Individual foods & nutrients linked to health risks

Diet patterns may be more informative
  – Diet indices estimated using enrollment food frequency questionnaire

Healthy Eating Indices

Dietary Approaches to Stop Hypertension (DASH) diet associated with 22% lower breast cancer risk; 40% lower for ER-negative cancer

Mediterranean Diet also associated with lower risk

Healthy Eating Index (multiple versions) and associated with lower breast cancer risk

*Petimar et al., Am J Clin Nutr 2019; Park et al., in preparation*
Dietary Patterns and Breast Cancer Risk

Mechanistic diets

Developed using data on biologic effects of specific nutrients in foods

**Dietary Inflammatory Index (DII)\textsuperscript{TM}**

- Pro-inflammatory diet associated with increased risk of ER- and triple negative breast cancer

**Oxidative Balance Score**

- Antioxidant diet associated with reduced risk of Triple negative breast cancer

Breast cancer risk for highest vs. lowest quartile of dietary index

*Park et al., Int J Cancer 2021*
Exposure to Ambient Light at Night (ALAN) and Obesity

Self-reported exposure to any indoor light, especially sleeping with light or TV on, associated with increased obesity at enrollment (BMI, waist circumference, other).

Sleeping with a light or TV on in the room associated with incident weight gain and obesity

Incident Obesity and Indoor Light at Night

Park et al., JAMA Intern Med 2019
Exposure to Light at Night and Hypertension

**Sleeping with light/TV** on in room associated with prevalent and incident hypertension

**Outdoor light** at night (satellite data), suggestively associated with *incident hypertension only among those reporting outdoor light in room while sleeping*

- Sleeping with light or TV on associated with breast cancer (HR 1.09, 95% CI 0.97, 1.23)
- After adjusting for correlated ambient exposures, outdoor light *not* associated with breast cancer

*Park et al., 2019 in preparation; Sweeney et al., Environ Int 2022*
Hypertension Prevalence and Exposure to Airborne Metals

Cross-sectional study of 10 airborne metals and hypertension using 2005 National Air Toxics Assessment data

- Hypertension = BP medication or systolic pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg

Arsenic, cadmium, cobalt, lead associated with increased risk; selenium associated with reduced risk

Metal mixture (without selenium) associated with small increase in risk

- OR 1.03 (95% CI 1.00, 1.06) per quartile increase (quantile-based g-computation)

J Xu et al., Environ Research 2020
9 airborne pollutants from 2005 National Air Toxics Assessment (NATA) database and NO$_2$ from 2005 monitoring data

Fossil fuel/Combustion/NO$_2$ mixture (quantile-based g-computation) mixture associated with hypertension

- PR 1.02, 95% CI 1.01, 1.04 per quartile increase
- PR 1.08, 95% CI 1.04, 1.12 among non-White participants
Hypertension Risk and Neighborhood Disadvantage

Neighborhood SES associated with mortality and chronic diseases

Evaluated SES and hypertension risk using the Area Deprivation Index (ADI)
- 17 measures from Census & Amer Comm Survey
- Ranks U.S. Census block groups by percentiles

Half of Sister Study participants live in a neighborhood with ADI ≤ the US 29th percentile – low deprivation

Kind et al., NEJM 2018
Increasing Neighborhood Deprivation (ADI*) Associated with Methylation-based Age Acceleration

Several “clocks” also associated with increased breast cancer risk

Kresovich et al., JNCI 2019

*Area Deprivation Index; Kind et al., NEJM 2018

Lawrence et al., JAMA Network Open 2020
Green Space Reduces Odds of Depressive Symptoms in Historically Redlined Neighborhoods

Adjusted Odds Ratio of depression* given a 10% increase in Tree Canopy

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Homeowner’s Loan Corporation (HOLC) Investment Risk Grade; A=Best, B=Still desirable, C=Declining, D=Hazardous (Redlined)

*Depression = CES-D 10 score ≥ 10

Tsai et al., in review
Final Thoughts and Sister Study Plans

Prospective cohort studies valuable for studying environment and health outcomes; need more diverse cohorts

New technologies have expanded options for exposure assessment, but questionnaires sometimes the best/only way to capture personal or historical/early life exposures
  – Where possible, validate with GIS, monitoring or biomarker/’omics data

Study impacts of multiple exposures; chemical mixtures; external and internal exposome

Don’t overlook the social and community environment

Recent and future Sister Study work addressing exposure and disparities
  – Metabolomics and diabetes in Black and White women
  – Racism and metabolic health/poor sleep

Increase focus climate change (e.g., heat waves, wildfires, flooding)
  – Improve environmental GIS databases; develop new exposure metrics
  – Focus on relevant exposure windows and geospatial resolution
  – Account for exposure variability over timer time
Sister Study Co-investigators

Clarice Weinberg
Katie O’Brien
Jack Taylor
Chandra Jackson
Alexandra White

https://www.sisterstudy.niehs.nih.gov