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





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



The Sister Study – Overview of Data Collection



4,427 incident breast cancer cases through Oct.12, 2020

Allows study of subtypes and population subgroups

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

Other Incident Cancers and Conditions



Other Conditions



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



Epigenetic mechanisms affected by

Epigenetics

- 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





Early Life Exposures and Breast Cancer Risk



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



Moderate early life trauma



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 <u>premenopausal</u> breast cancer

Frequent use in **year before enrollment** associated with 50% increase in *postmenopausa*l 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

Adolescent Hair Straightener Use & Premenopausal Breast Cancer Risk



Current Hair Straightener Use & Postmenopausal Breast Cancer Risk



Air Pollution and Breast Cancer Exposures and effects may vary by region

 $\rm NO_2$ consistently associated with breast cancer risk but evidence for $\rm PM_{2.5}$ mixed

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

<u>Reding 2015</u>: NO₂ associated with ER+ breast cancer [**RR 1.10** (95% CI 1.02, 1.19 per IQR]; no association with PM_{2.5}

<u>White 2019</u>: 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



Air Pollution and Invasive Breast Cancer Stratified by U.S. Region



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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

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<u>Dietary Approaches to Stop Hypertension (DASH)</u>
diet associated with 22% lower breast cancer risk;
40% lower for ER-negative cancer
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Mediterranean Diet also associated with lower risk

<u>Healthy Eating Index (multiple versions)</u> and associated with lower breast cancer risk

Petimar et al., Am J Clin Nutr 2019; Park et al., in preparation





Park et al., Int J Cancer 2021

Dietary Patterns and Breast Cancer Risk

Anti-inflammatory

Mechanistic diets

Developed using data on biologic effects of specific nutrients in foods

<u>Dietary Inflammatory Index</u> (DII)[™]

 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





Pro-inflammatory

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

Relative risk

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 <u>incident</u> <u>hypertension only among those reporting</u> <u>outdoor light in room while sleeping</u>

- 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

Indoor Light at Night and Hypertension at Enrollment

Adjusted for Confounders Adjusted for Potential Mediators





Any ALAN exposure

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 gcomputation)

Hypertension and metals

		N	OR(95%CI)	
Arsenic(As)	Quartile 1	11898	1 (referent)	-
	Quartile 2	11898	1.05(0.99,1.11)	⊧ +
	Quartile 3	11901	1.08(1.02,1.15)	⊢
	Quartile 4	11898	1.10(1.04,1.17)	⊢
	p for trend		0.002	
Cadmium(Cd)	Quartile 1	11898	1 (referent)	
	Quartile 2	11899	1.02(0.97,1.09)	⊢ ∎1
	Quartile 3	11900	1.09(1.02,1.15)	F€
	Quartile 4	11898	1.00(0.94,1.06)	⊢ ,
	p for trend		0.74	
Cobalt(Co)	Quartile 1	11898	1 (referent)	-
	Quartile 2	11900	1.04(0.98,1.10)	P₽1
	Quartile 3	11898	1.07(1.01,1.14)	⊢
	Quartile 4	11899	1.07(1.01,1.13)	⊢ ∎i
	p for trend		0.09	
Lead(Pb)	Quartile 1	11897	1 (referent)	
	Quartile 2	11901	1.09(1.02,1.15)	⊢
	Quartile 3	11899	1.04(0.98,1.11)	F 1
	Quartile 4	11898	1.10(1.04,1.17)	⊢_ ∎ ;
	p for trend		0.01	
Selenium(Se)	Quartile 1	11898	1 (referent)	
	Quartile 2	11900	1.00(0.94,1.06)	⊢
	Quartile 3	11899	1.04(0.98,1.11)	⊢₽1
	Quartile 4	11898	0.91(0.86,0.97)	⊢
	p for trend		0.001	
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Fossil-fuel and Combustion-related Air Pollution & Hypertension



0.95

1.15

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Xu J, et al., Env Poll 2022

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





Prevalence Ratio and 95% CI

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



*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 of depression^{*} given a 10% increase in Tree Canopy 500m Buffer 2000m Buffer Adjusted Odds Ratio 1.0 1.01 0.97 0.97 0.94 0.93 0.93 0.92 0.90 0.72 0.63 0.4 Overall D Overall С Α В С В D Α HOLC Grade HOLC Grade

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

*Depression = CES-D 10 score \geq 10

Tsai et al., in review



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





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