Understanding the Association Between Air Pollution and Breast Cancer

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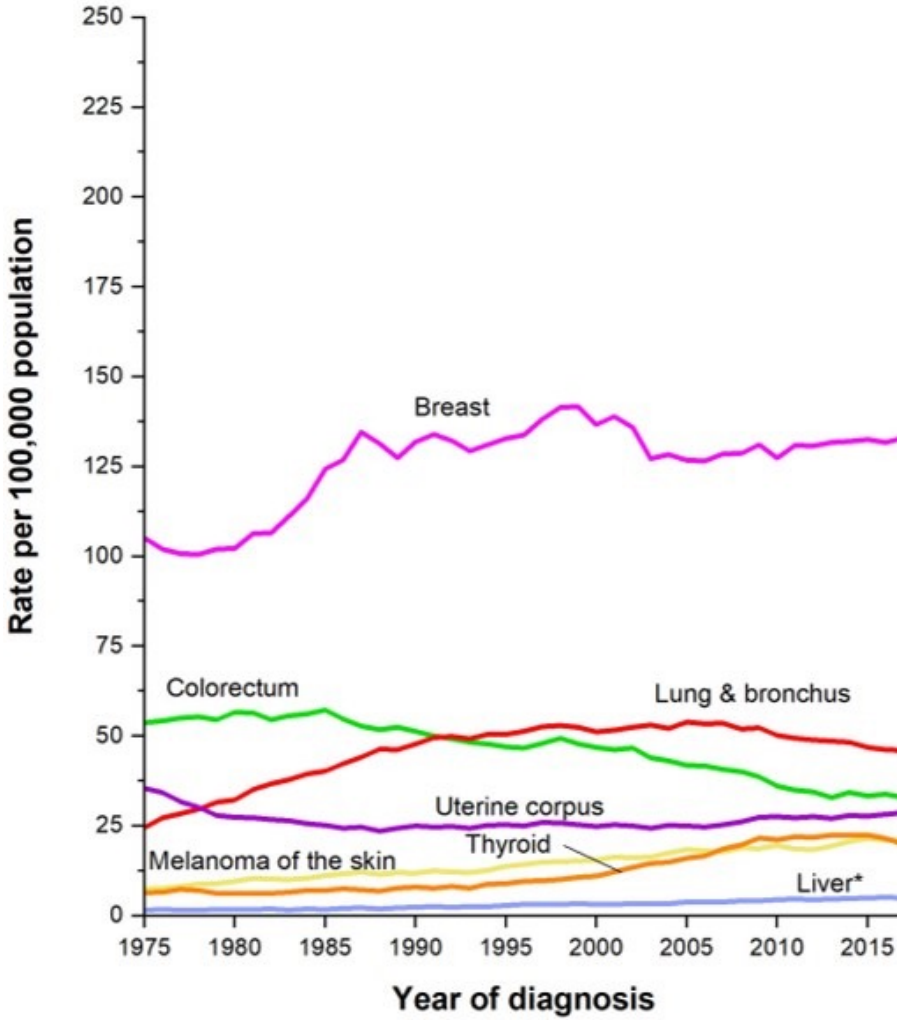
Breast Cancer Epidemiology

Most commonly diagnosed cancer among women in the US and worldwide

- In 2022, ~287,000 US cases

Risk factors and survival vary by

- Menopausal status
- Tumor subtypes defined using the hormone receptors estrogen (ER) and progesterone (PR)



WHO 2021; ACS facts and figures 2019-2021; Jemal et al., 2022

Established Breast Cancer Risk Factors

Relative Risk	Risk Factor
>4.0	Age (65+ vs <65) Genetic variants (*BRCA1, BRCA2*)
2.1-4	Mammographically dense breast High-dose radiation
1.1-2.0	1 first degree family member with breast cancer Postmenopausal obesity Lack of physical activity Alcohol consumption Early age at menarche Late age at first full term birth Later age at menopause No breastfeeding

Environment?

Most established risk factors for breast cancer have modest effect sizes

Air pollution

WHO, 2016

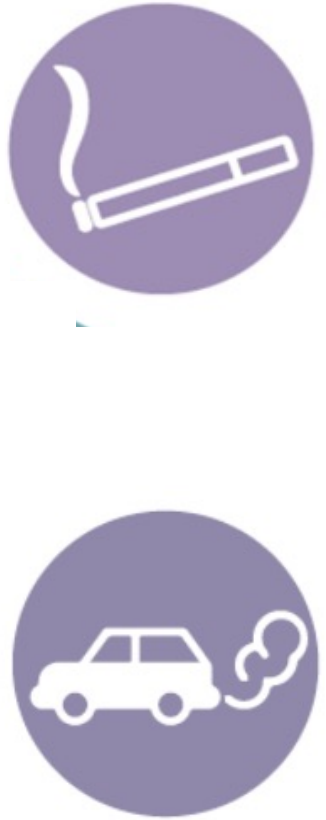
Air pollution may be related to breast cancer

Air pollution is a carcinogenic exposure

- Outdoor air pollution is classified as a Group 1 carcinogen
- Inhaled toxicants have been found in breast fluid

Complex, heterogenous mixture of carcinogenic and endocrine disrupting compounds

- Polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds and metals



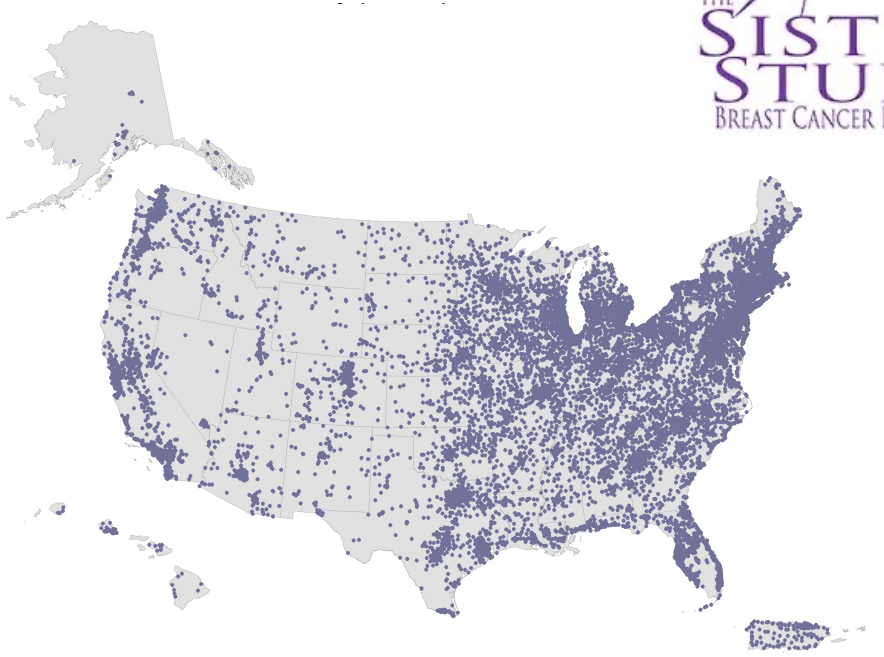
IARC 2013; Hill et al., 1979; el-Bayoumy et al., 1995; Huff et al., 1989; Gabet et al., 2021

Air pollution and Breast Cancer Risk

Sister Study

Prospective cohort study (n=50,884)

- Recruitment from 2003-2009
- Eligibility criteria:
  - Breast cancer-free women
  - Ages 35-74
  - Residents of the U.S. and Puerto Rico
  - Sister diagnosed with breast cancer
- Completed extensive questionnaire at baseline



Follow-up

- Annual health updates and biennial surveys
  - Response rates ≥90% over follow-up
- Diagnoses confirmed by medical record and pathology reports

Average follow-up	10.5 years
Total Cases	3,984
Invasive cases	3,120
DCIS	850
ER+	2,896
ER-	508

Sister Study Baseline Characteristics

Median age was 55.6 years

84% non-Hispanic White, 9% non-Hispanic Black/African American

51% bachelor's degree or higher

33% annual household income >$100,000

Airborne metals and breast cancer

Hazardous air toxics

- Group of pollutants that are expected to have adverse health effects

Certain metals are classified as probable carcinogens

- Arsenic, cadmium, chromium, nickel, lead, copper and mercury

“Metalloestrogens”- hypothesis that certain metals ability to activate estrogen receptor (ER)

- Proliferation of estrogen-dependent breast cancer cells
- Increase expression of estrogen-regulated genes

Metals have been measured in the breast tissue

IARC, Siddiqui et al., 2006, Martin et al., 2003, Byrne et al., 2013

National Air Toxics Assessment

EPA's 2005 National Air Toxics Assessment (NATA) database

Nationwide census-tract levels of air toxic pollutants including metals

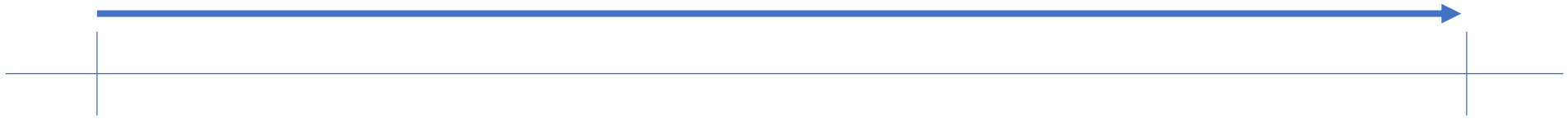
- Relies on inputs from the National Emissions Inventory, exposure modeling

Airborne metals and breast cancer risk

Study aim: Evaluate the association between ***airborne metals*** (individually and as a mixture) at study baseline and ***breast cancer risk***

- Arsenic, cadmium, chromium, cobalt, lead, mercury, manganese, nickel

~7.4 years of follow-up, N=2,587 incident breast cancer cases

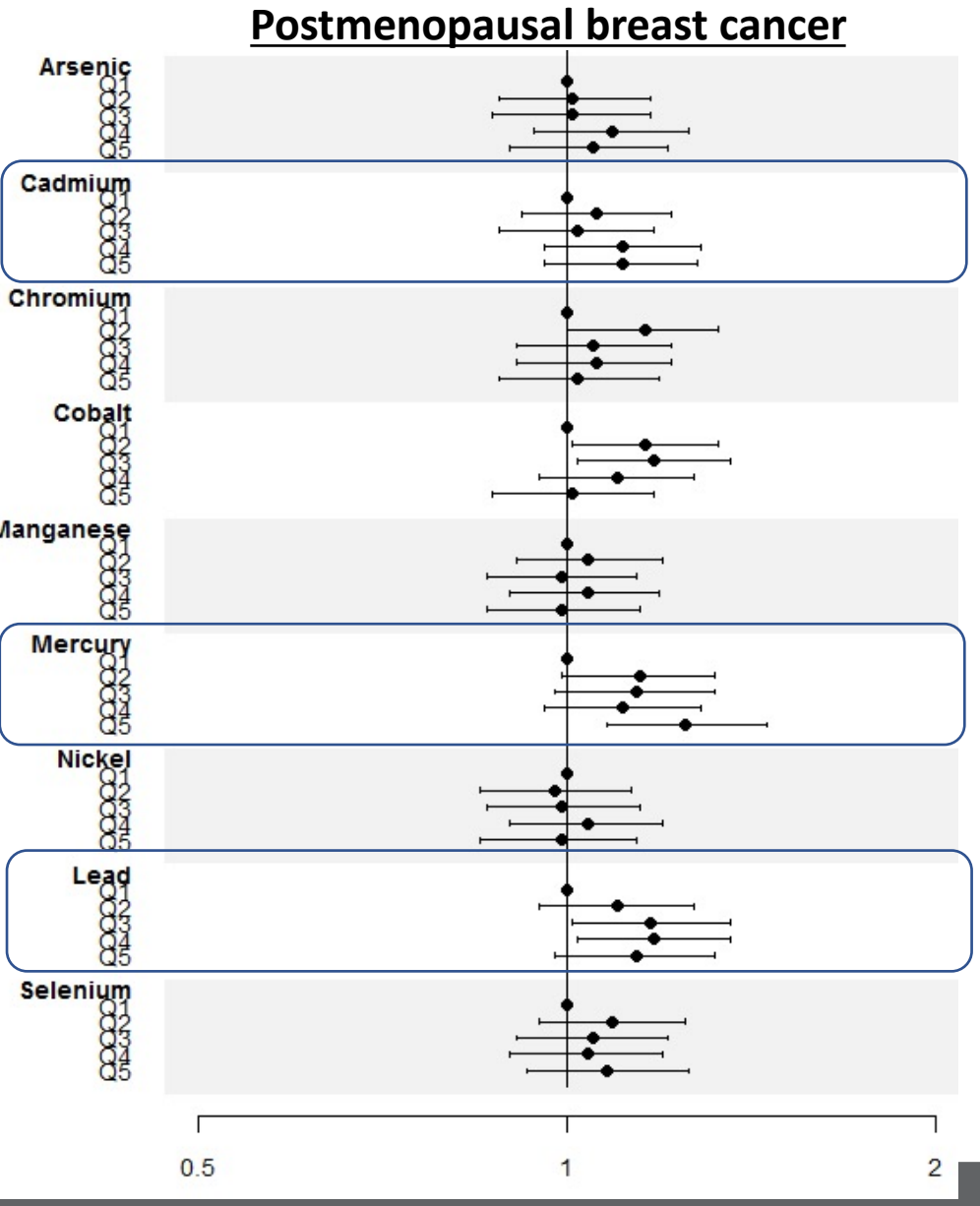


2003-2009
Sister Study enrollment

Geocoded addresses linked to 2005 NATA

July 31st, 2015
End of Follow-up

Airborne metal mixtures and breast cancer risk



No associations with overall breast cancer risk or by ER tumor subtype

Postmenopausal breast cancer: elevated HRs for mercury, lead, cadmium

Mixtures approach: weighted quantile sum to evaluate the association for increasing all metals by a quintile

- Overall mixture effect? 10% higher risk for postmenopausal breast cancer
- Toxic Agents? Driven by cadmium, lead, mercury, cobalt

Adjusted for race, education, income, marital status, census income, region

White et al., 2019 *Epidemiology*

Findings in context

First study to consider metal mixtures in relation to breast cancer risk

- California Teacher's Study - higher airborne Cd and As related to risk of ER-PR-

Cadmium, lead and mercury

- Cadmium as a metalloestrogen
- Suggests a role for industrial emissions
  - Sources: coal burning, municipal waste incineration, metal processing

Limitations

- NATA relies on reported data to produce modeled estimates of exposure, does not incorporate monitoring data
- Criteria pollutants have better exposure assessment methods

Criteria pollutants and breast cancer risk

Criteria pollutants are common air pollutants that are more frequently monitored by the EPA

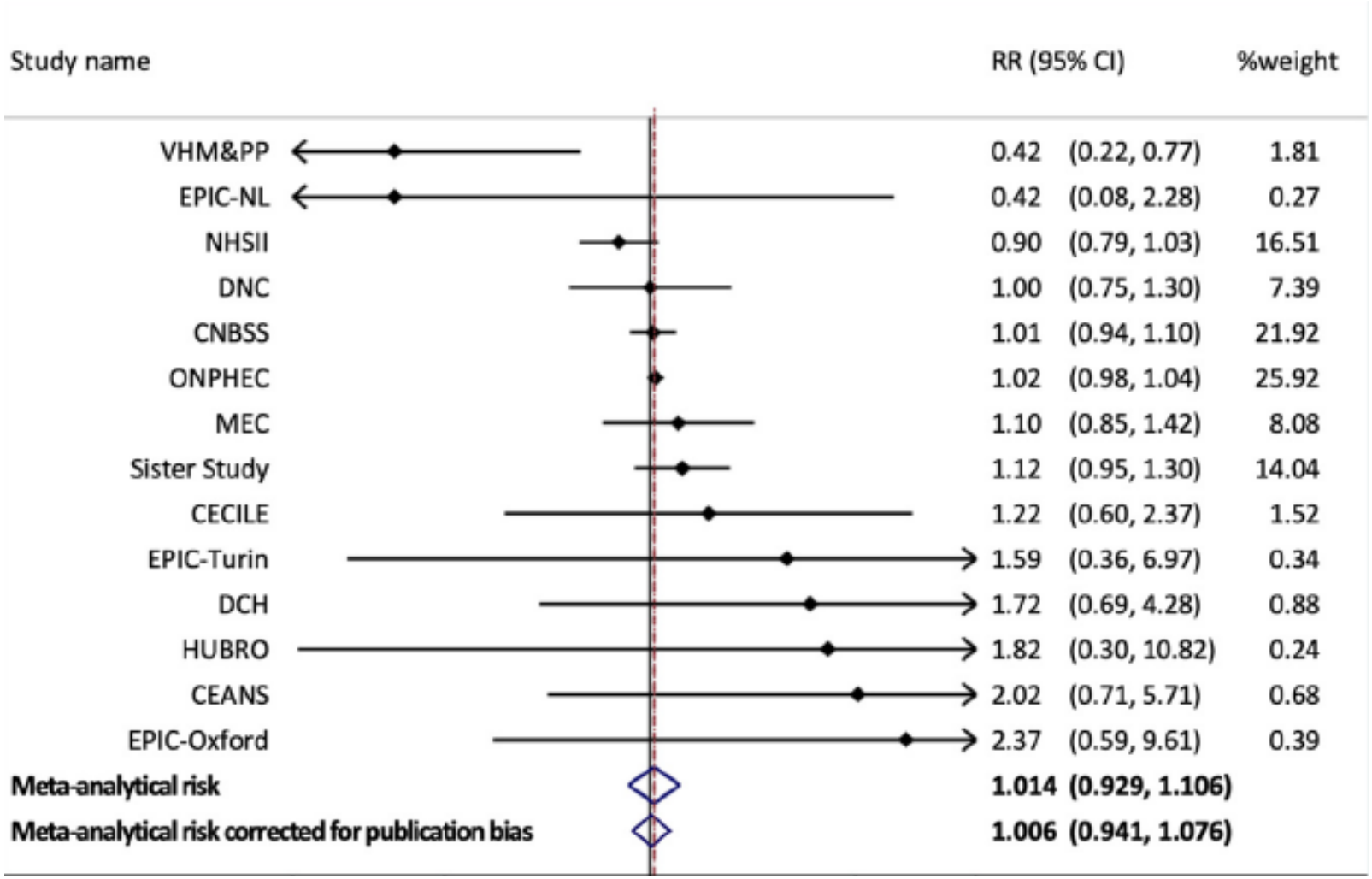
- Particulate matter (PM), nitrogen dioxide (NO_2), ozone

For breast cancer, evidence from population-based studies has been inconclusive

- Markers of traffic-related pollution (NO_2) tend to be positively related to breast cancer risk
- Largely null associations observed for particulate matter (PM)

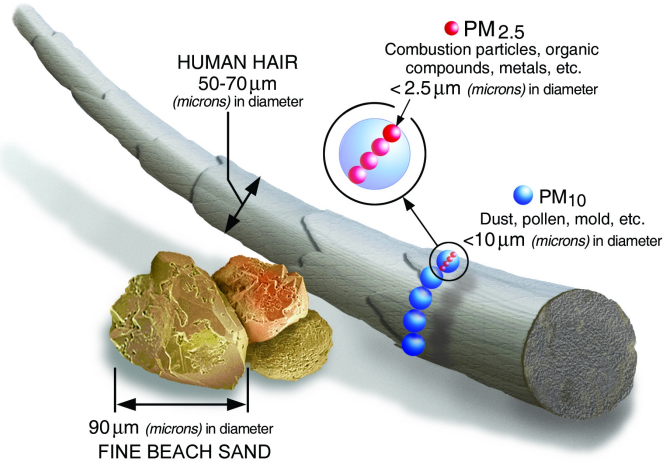
White et al., 2018; Andersen et al., 2016; Andersen et al., 2017; Reding et al., 205; Hart et al., 2016

$PM_{2.5}$ not associated with breast cancer



PM aggregate measure based on particle size

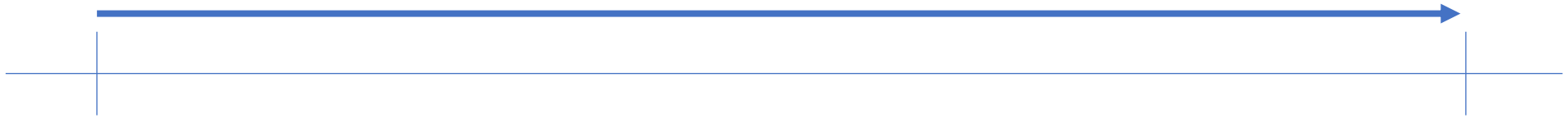
- Geographic variability in composition
- Varying exposure sources



Criteria pollutants and breast cancer risk

Study aim: Evaluate the association between ***criteria pollutants*** (NO_2, PM_{10} and $PM_{2.5}$) and $PM_{2.5}$ component mixtures at study baseline and ***breast cancer risk***

~8.4 years of follow-up, N=2,852 incident breast cancer cases



2003-2009
Sister Study enrollment

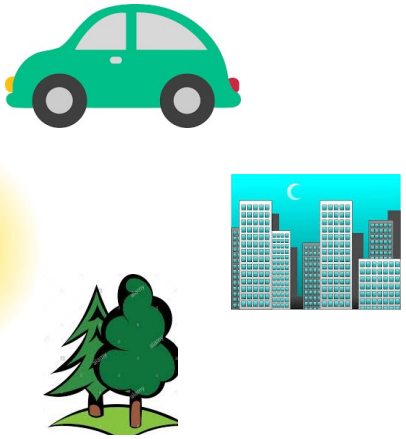
Geocoded addresses linked to air pollution exposure models

Sept 15th, 2016
End of Follow-up

Exposure Assessment: $PM_{2.5}$, PM_{10} and NO_2

EPA Monitoring Data

2006 ($PM_{2.5}$, NO_2)
2000 (PM_{10})



Geographic Covariates

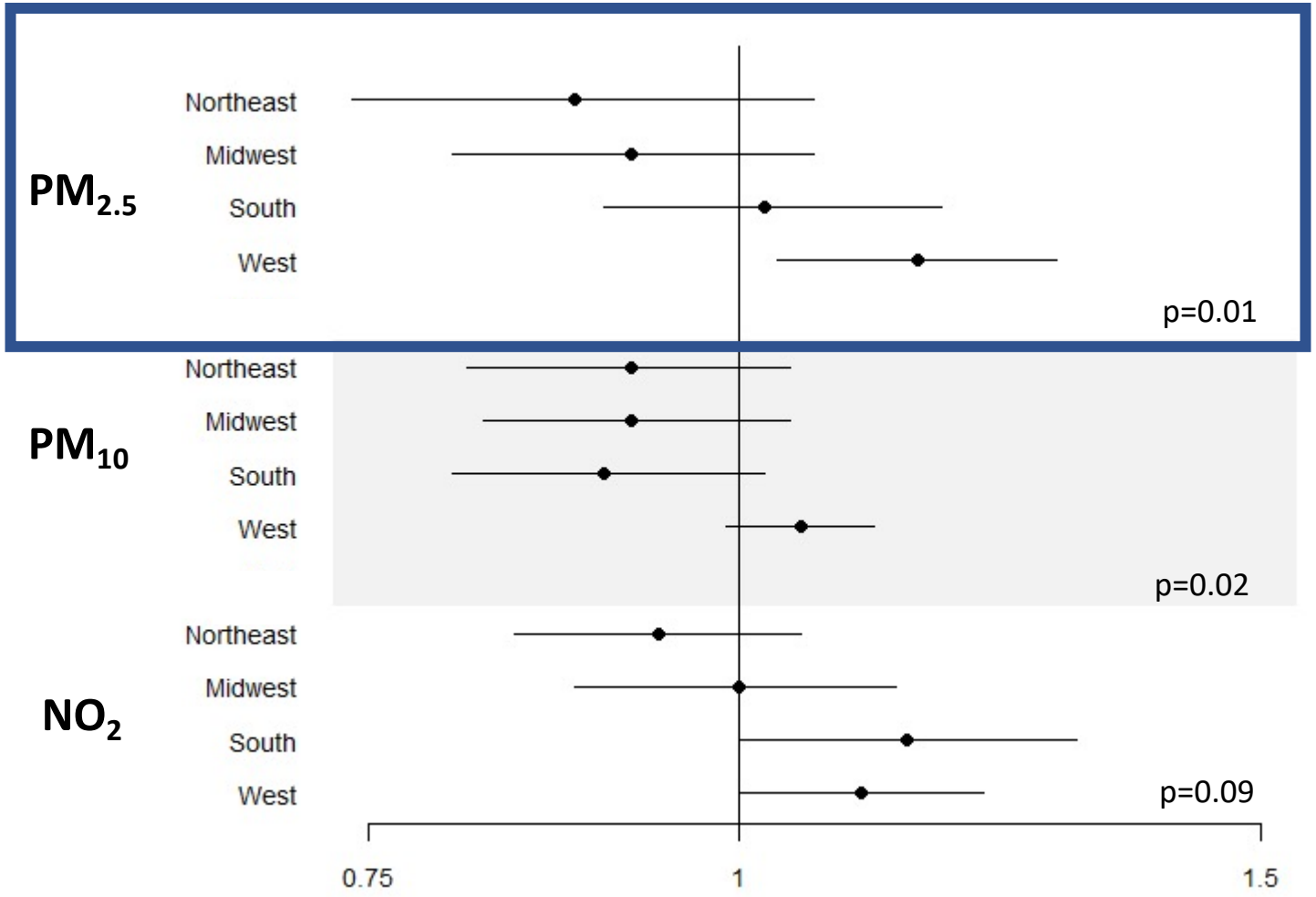
Validated regionalized universal kriging model with spatial smoothing

Annual Average

Limited to women living in the contiguous US (n=49,771)

Sampson et al., 2013; Young et al., 2016

Air pollution and breast cancer risk, by region



IQRs: $PM_{2.5}$=3.6 $\mu g/m^3$
PM_{10}=5.8 $\mu g/m^3$
NO_2=5.8 ppb

Invasive breast cancer

*heterogeneity p values

Sister Study (N=50,884, N=3,002 cases)

Criteria pollutants ($PM_{2.5}$, PM_{10} and NO_2)

Substantial geographic heterogeneity

- For $PM_{2.5}$, this was explained in part by $PM_{2.5}$ component profiles

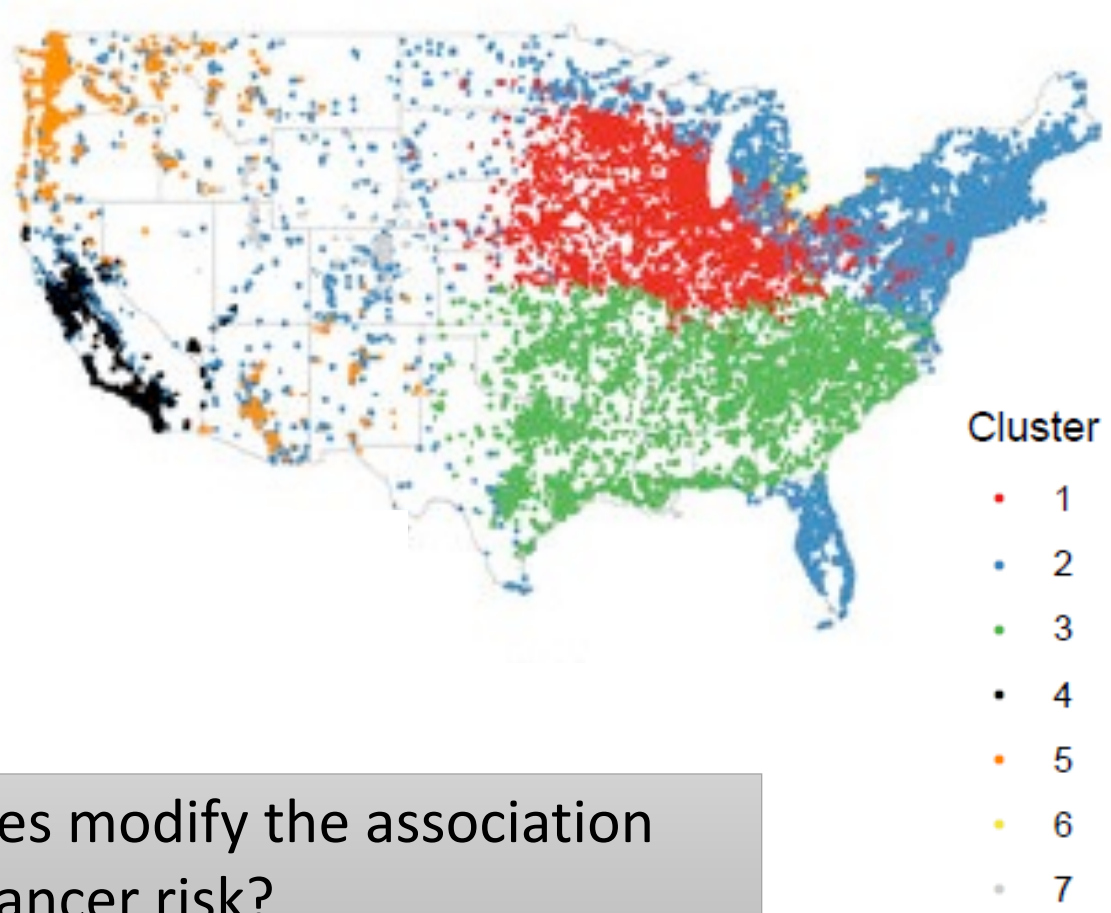
White et al., 2019 EHP

Adjusted for age, race/ethnicity, smoking status, hormone therapy

$PM_{2.5}$ component clusters

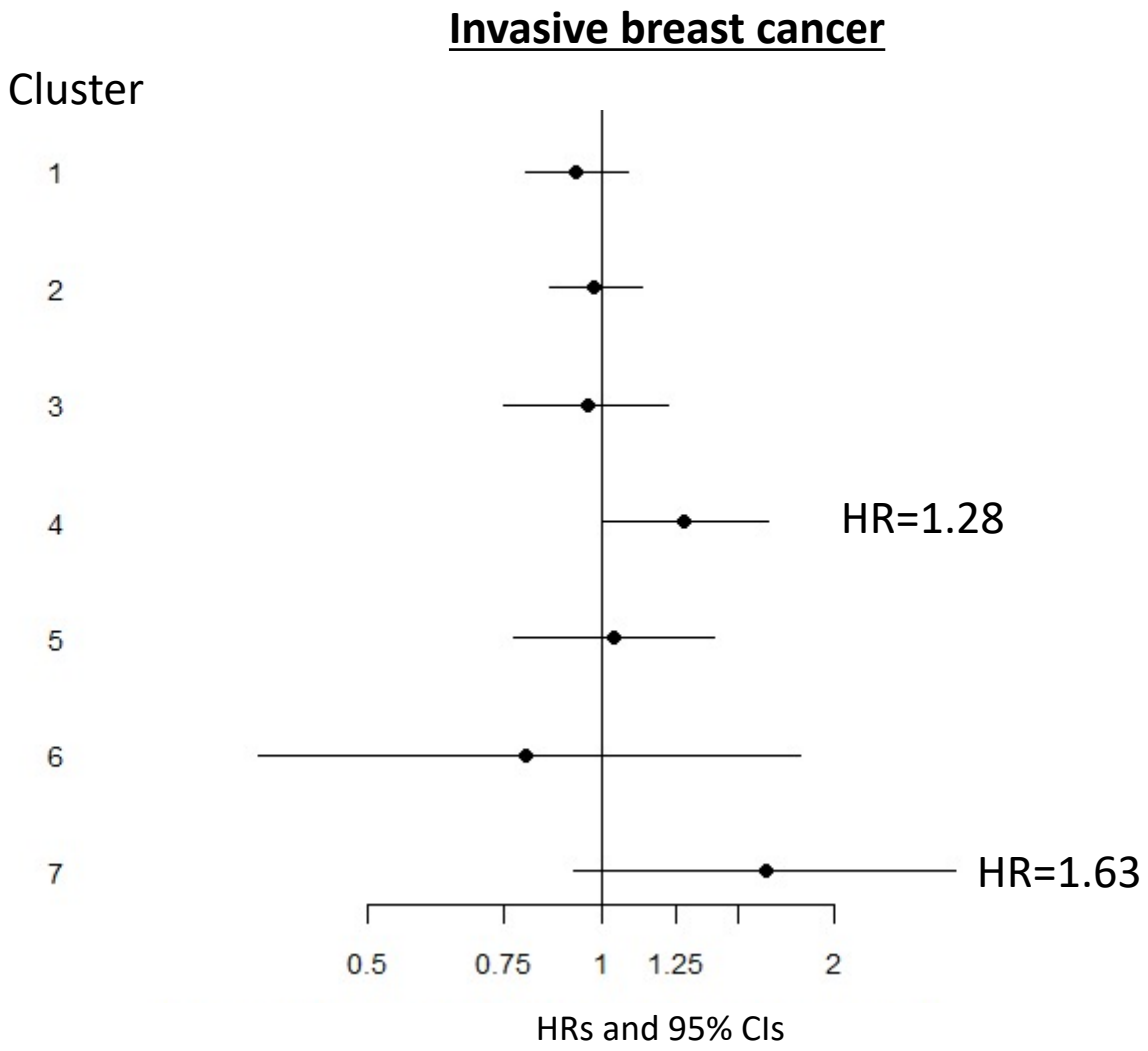
Identified subgroups of women with ***similar $PM_{2.5}$ component profiles*** using k-means covariate adaptive clustering

- Overall $PM_{2.5}$ mass does not substantially vary across cluster
- Varying chemical component profiles can be used to identify important $PM_{2.5}$ sources



Does the $PM_{2.5}$ component profiles modify the association between total $PM_{2.5}$ and breast cancer risk?

$PM_{2.5}$ and breast cancer, by $PM_{2.5}$ component clusters



- **Cluster 4:** low sulfur and high sodium and nitrate → agricultural emissions
- **Cluster 7:** high Si, Ca, K, and Al → surface soil in the Western US

White et al., 2019 EHP

Findings in context

First study to consider $PM_{2.5}$ mixtures in relation to breast cancer risk

- Important given the differences in $PM_{2.5}$ composition across the US
- Prior studies that evaluated $PM_{2.5}$ over large geographic areas may have masked over relevant heterogeneity in the associations → could explain largely null findings

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Explore $PM_{2.5}$ heterogeneity in another large US-wide population?

- Black Women's Health Study
  - Black women tend to live near more carcinogenic sources of air pollution and are more likely to be diagnosed with more aggressive subtypes (e.g., hormone receptor negative breast cancer)

Morello-Frosch and Jesdale 2006, Carey et al., 2006

Air pollution and breast cancer, by region

Black Women's Health Study (N=41,317, N=2,146 overall breast cancer cases)

- Residential exposure to $PM_{2.5}$, NO_2, O_3

Higher air pollution was not related to breast cancer risk overall

Geographic heterogeneity for $PM_{2.5}$

- Higher overall breast cancer risk for women living in the Midwestern US

$PM_{2.5}$ and breast cancer risk, by geographic region

Geographic Region	HR (95% CI)
Northeast	0.95 (0.79-1.15)
South	0.89 (0.78-1.02)
Midwest	1.18 (1.00-1.39)
West	0.97 (0.91-1.03

HR for a unit increase in the IQR $PM_{2.5}$=2.9 $\mu g/m^3$

White et al., 2021 Envr Res

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Explore this heterogeneity in another large US-wide population?

- Black Women's Health Study – $PM_{2.5}$ association varied by geographic region
  - BWHS air pollution exposure assessment only in metropolitan areas
  - Sister Study is a population of women with a family history of breast cancer

Enriched population

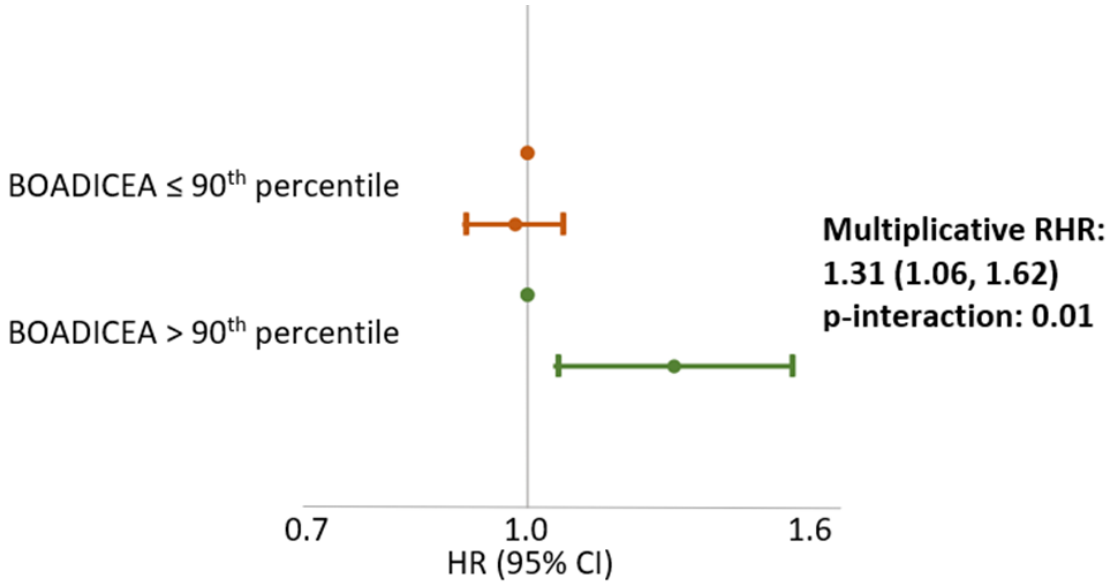
By enrollment criteria, Sister Study participants have underlying familial risk

- More susceptible to exposures?
- Extent of family history → reduced expression of certain DNA repair genes

Air pollution-breast cancer association stratified by extent of family history

- Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) – incorporates family history information

NO_2 associated with a 30% higher risk of breast cancer in high familial risk women



Niehoff NM… White AJ (senior), AJE 2022

Kapil et al., 2016

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Limitation: focus on exposure during cohort enrollment

- Historic exposure to $PM_{2.5}$?

Historic $PM_{2.5}$ and breast cancer risk, NIH-AARP

NIH AARP Diet and Health Study (N=226,733 women, 13,246 breast cancer cases)

- Enrolled in 1995/1996
- Residential $PM_{2.5}$ exposure 1980-1984

Observed a higher risk of breast cancer overall and for ER+ tumors

Significant variability across the various catchment areas

$PM_{2.5}$ and breast cancer risk, by type

Breast Cancer Type	HR (95% CI)
Overall	1.07 (1.01-1.13)
ER+	1.09 (1.02-1.17)
ER-	0.97 (0.80-1.17)

White et al., in progress (preliminary data)

Findings in context

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- Historic exposure to $PM_{2.5}$?

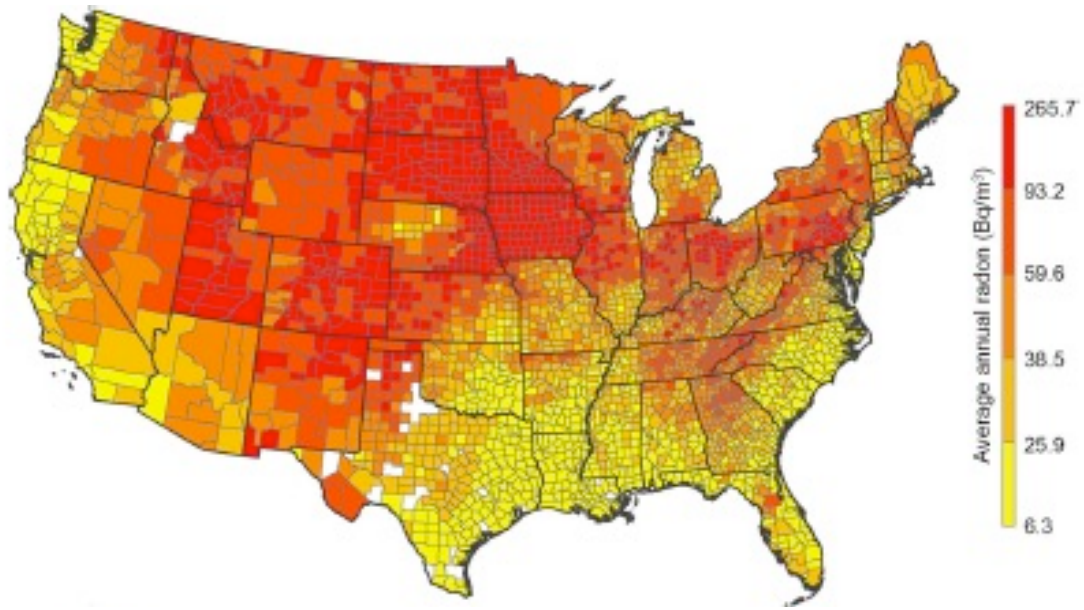
Other carcinogenic attributes of $PM_{2.5}$?

- Radioactivity of fine particles

Radioactivity of fine particles

Understudied aspect of air pollution carcinogenicity

Radon is a naturally-occurring source of ionizing radiation, varies geographically across the US



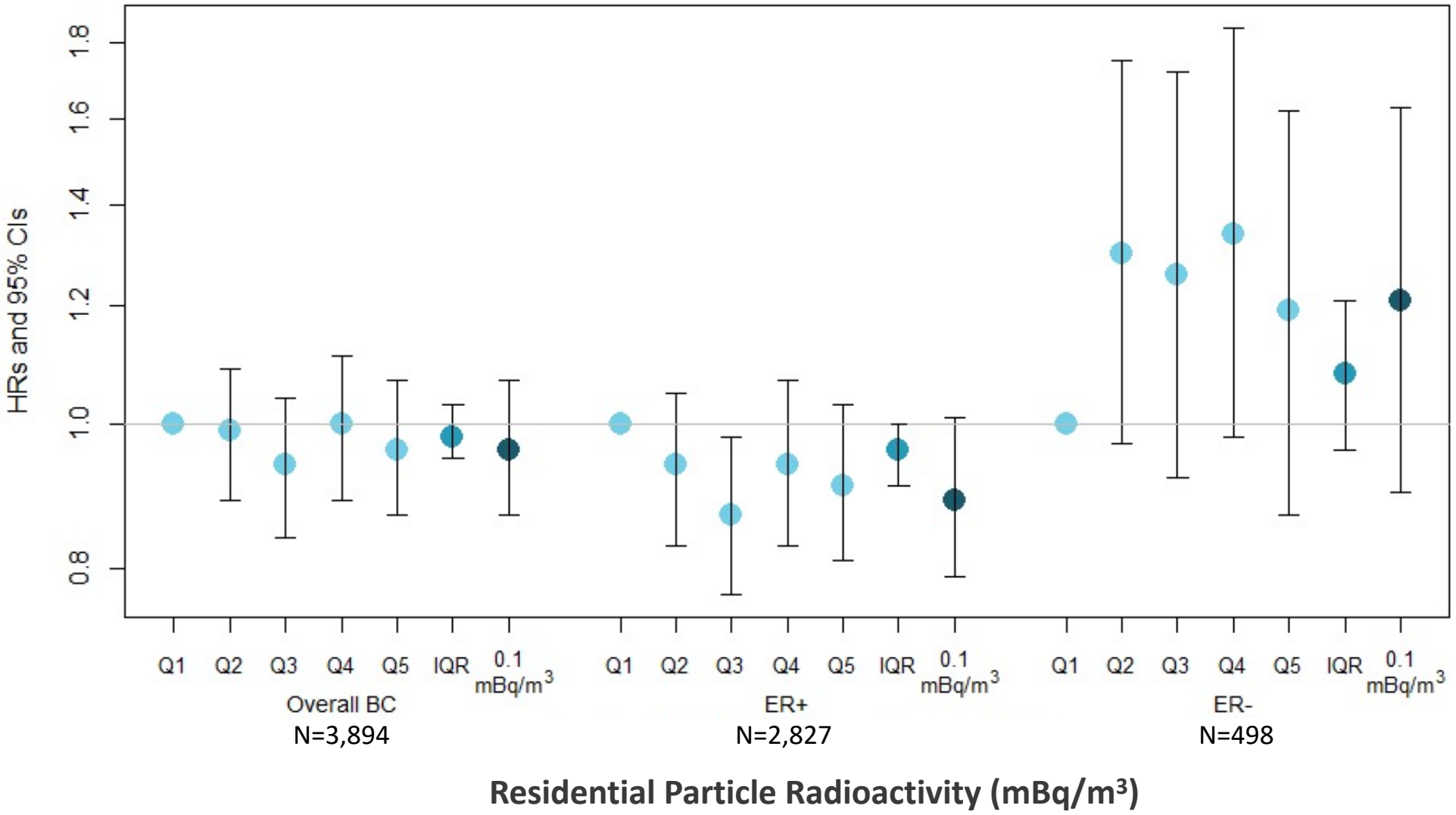
PM can be a vector for radioactive isotopes

- Radon decay products can attach to $PM_{2.5}$ particles
- After being inhaled and deposited in the lungs, progeny can release radiation

Particle radioactivity associated with oxidative stress and inflammatory biomarkers, but no study yet has considered associations with cancer

IARC 1988, Bloomberg 2020, Ronckers et al., 2005; VoPham et al., 2017

Particle radioactivity and ER- cancer



Nationwide spatiotemporal ensemble model -- annual gross beta particle radioactivity (mBq/m^3) at a 32 km grid

In women who were residentially stable: ER- HR_{IQR}=1.15, 95% CI:0.99-1.34

White et al., EHP 2022

Air pollution and Breast Cancer: Summary

Airborne metal findings suggest industrial emissions may increase breast cancer risk

Studies also support a role for $PM_{2.5}$ in breast cancer etiology, when considering ***geographic heterogeneity in exposure*** and ***historic exposure***

- Women with a breast cancer family history may be more susceptible to air pollution exposure
- Particle radioactivity may be associated with ER- breast cancer risk

Future Directions

Pooled study: air pollution and women's cancers

Limitations of prior work

- Limited power for considering relevant subgroups (tumor subtype, premenopausal women)
- Consideration of a single adult address as a proxy for long-term exposure

Pooled cohort studies of air pollution and breast/ovarian cancer

- CVD R01 (Joel Kaufman, UW)
- State-of-the-art air pollution exposure models, improved temporal and spatial resolution
- Consideration of variation by subtype, menopausal status, geographic region, **race/ethnicity**

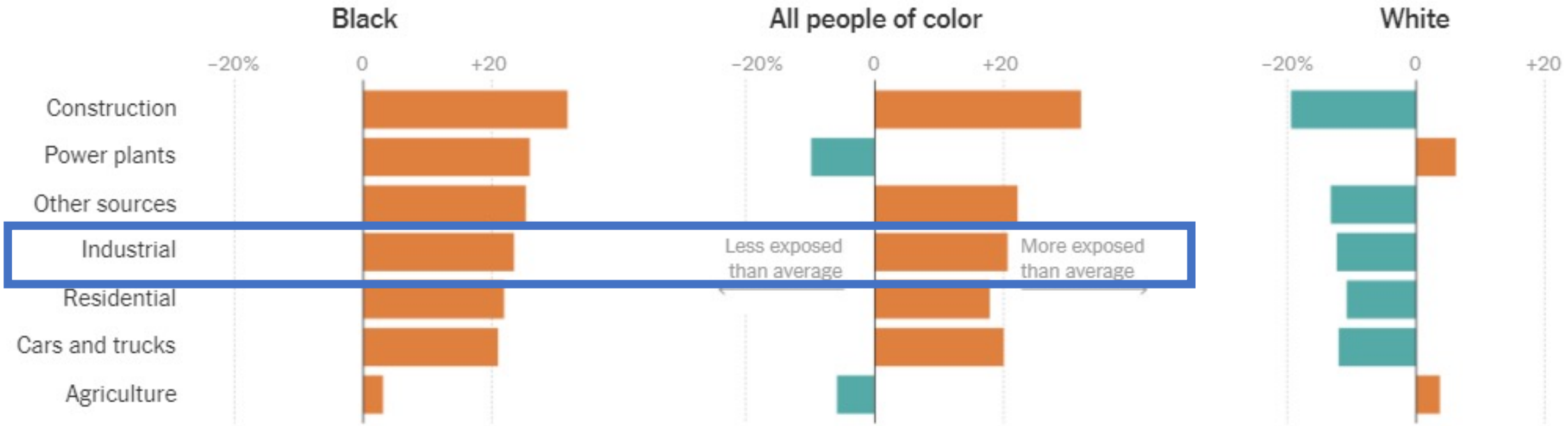
Table 1. Air pollution and women's cancers pooled study: individual cohort descriptions

Cohort	Study baseline year	Total Cohort N (without restrictions)	Follow-up schedule	Follow-up addresses
Nurses' Health Study I	1976	121,907	Every 2 yrs in person	1986-2006; 2008-2010
Nurses' Health Study II	1986	116,430	Every 2 yrs in person	1991-2005, 2007-2009
Women's Health Initiative Clinical Trial	1993	68,132	WHI has several Clinical Trial (CT) - arms, each with a differing follow-up schedule	Through 2018
Women's Health Observational Study	1993	93,676	Annual mailing	Through 2018
Sister Study	2003-2009	50,884	Annual update (mail)	Through 2018

Air pollution and Breast Cancer: health disparities

Biggest Pollution Disparities

Nationwide, Black people are exposed to greater-than-average concentrations of a dangerous form of pollution known as PM 2.5. People of color face more exposure from almost every type of source, while white people are less exposed.



Other sources include pollution from commercial cooking, off-highway vehicles and equipment, and others. The cars and trucks category includes direct pollution as well as road dust. • Source: Tessum et al., Science Advances • By The New York Times

Future Work – industrial emissions

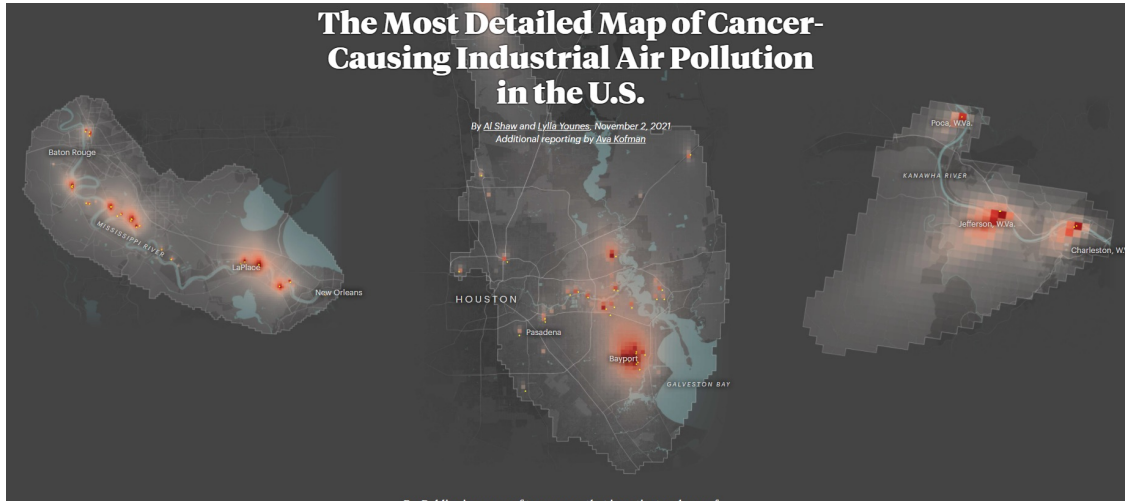
Point sources of industrial emissions and breast cancer risk

- EPA Toxics Release Inventory- residential exposure to industrial emissions in Sister Study
- Overall carcinogenic emissions
  - Consider disparities in exposure by both individual and neighborhood-level characteristics

ProPublica report on industrial air pollutants and cancer risk

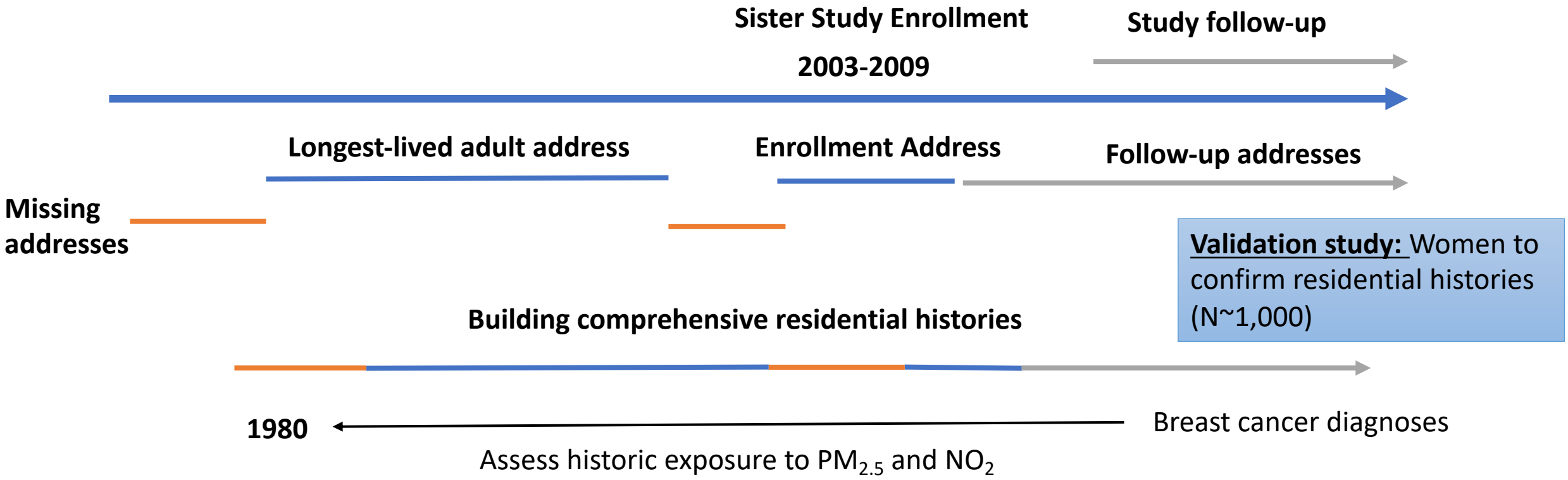
Existing EPA carcinogenic risk estimates lacks consideration of:

- impact of multiple exposures (mixtures)
- environmental justice



https://www.propublica.org/article/toxmap-poison-in-the-air

Historical air pollution and breast cancer



- Previous work has focused on relatively recent, adult-level exposure
- Capture air pollution exposure decades prior
  - During the *reproductive years* and the *menopausal transition* –hypothesized windows of susceptibility when the breast may be more susceptible to carcinogens

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Thank you!

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