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On the need to consider both Genetic Susceptibility Windows of Susceptibility (WOS) for environmental exposures and breast cancer

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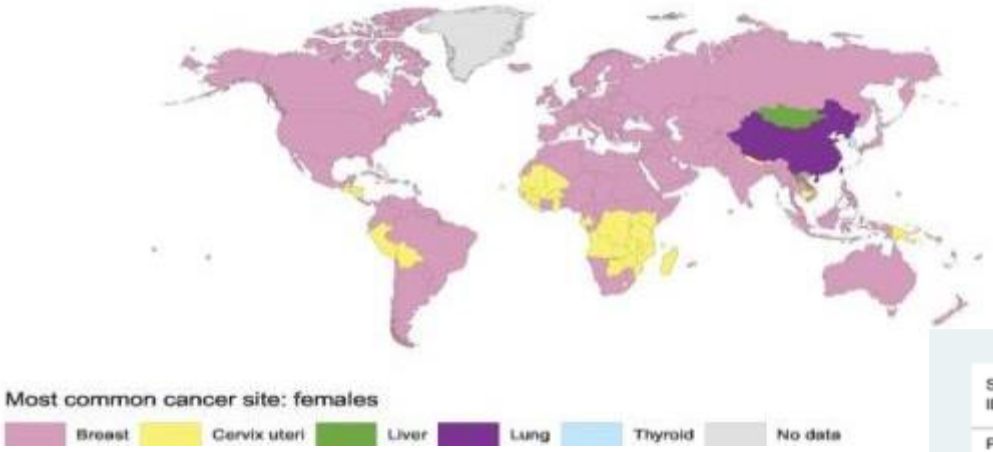
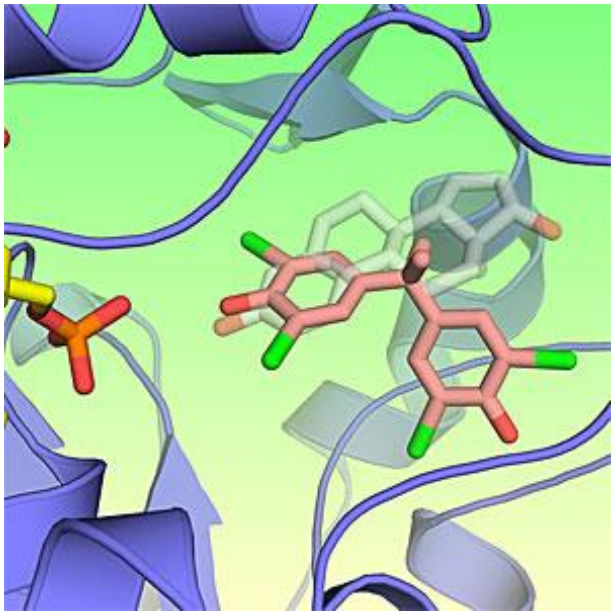
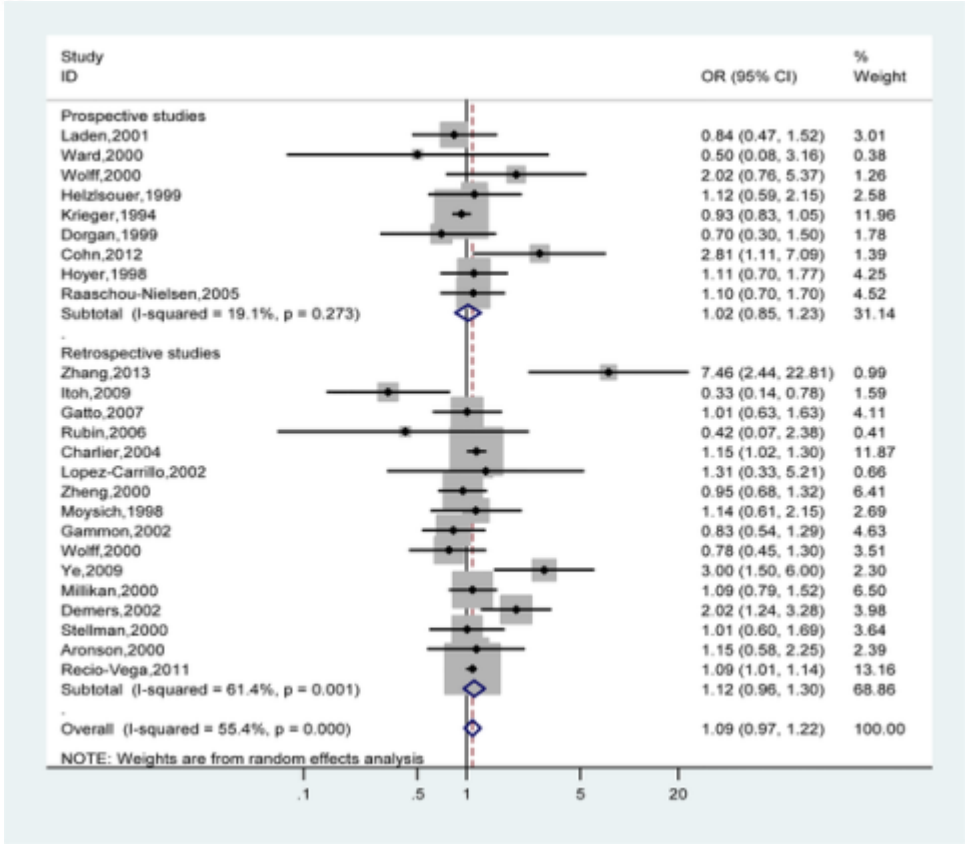
So what about the Environment and Breast Cancer?



Lindsey A. Torre et al. Cancer Epidemiol Biomarkers Prev 2016;25:16-27



Gosavi RA, Knudsen GA, Birnbaum, LS, Pedersen LC. EHP 2013

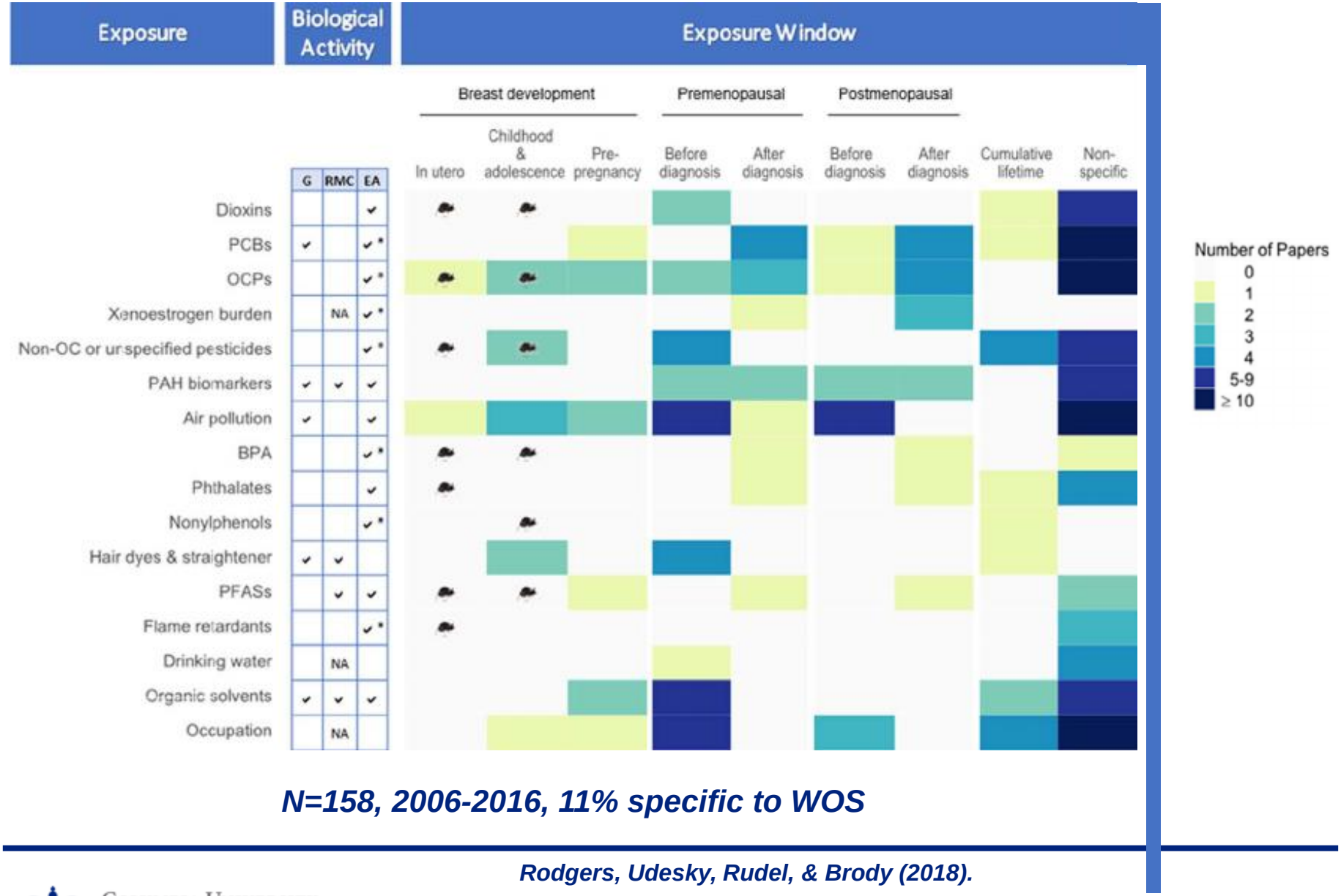


Zhang J, Huang Y, Link K, Wu K. PLOS ONE 2015

Most empirical evidence relatively modest

1) Most studies fail to factor in windows of breast cancer susceptibility

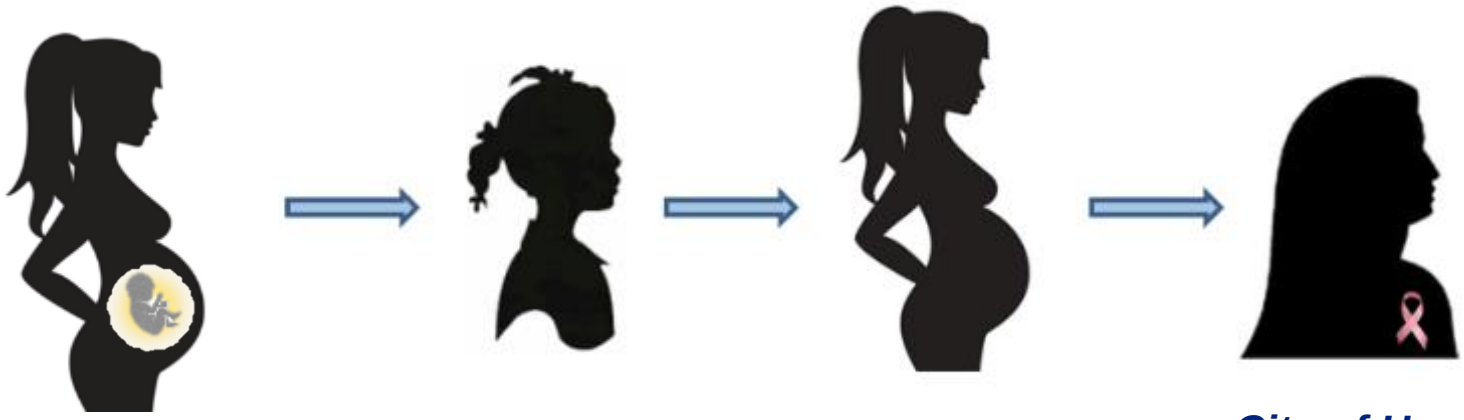
2) Most studies estimated in average risk cohorts



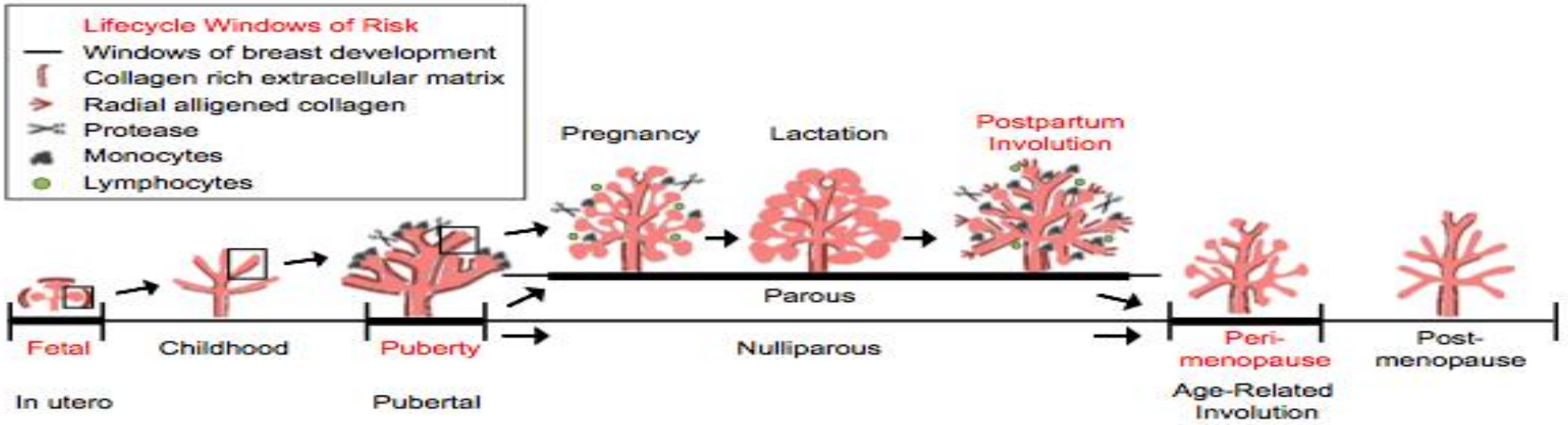
N=158, 2006-2016, 11% specific to WOS

Rodgers, Udesky, Rudel, & Brody (2018).

Windows of Susceptibility (WOS)



Columbia ***Michigan*** ***UCLA/Chile*** ***UMASS*** ***Columbia*** ***City of Hope*** ***Georgetown***



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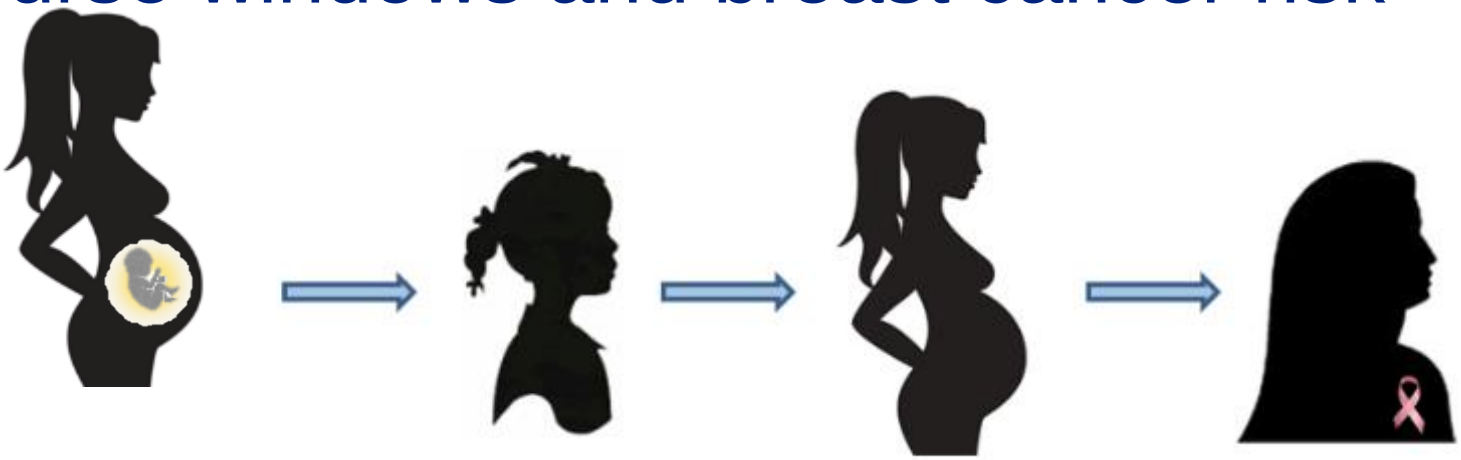
Martinson et al. Exp Cell Res. 2013

Life course windows and breast cancer risk



Regional total suspended particulates

Maternal o,p'-DDT

p,p'-DDT metabolites in serum taken after

16 serum PFAS during pregnancy including 10 PFCA, 5 PFSA, and PFOSA

Serum PCB during early postpartum

Urinary cadmium

Dietary cadmium

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BCERP Framework Paper Breast Cancer Research 2019.

Most empirical evidence relatively modest

1) Most studies fail to factor in windows of breast cancer susceptibility

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of publications : Family history (Type 1), Early onset breast cancer (Type 2), or genetic susceptibility (Type 3)

68 pubs in 36 unique studies.

Only 5.5% (2/36) Type 1
Only 11% (4/36) Type 2

Over 70% of the pubs from these 6 enriched studies were positive
Type 1: 7/9 pubs
Type 2: 6/8 pubs

Over 70% of Type 3 publications were positive in subgroups of women with greater genetic susceptibility

Variants in carcinogen metabolism, DNA repair, oxidative stress, cellular apoptosis and tumor suppressor genes

Type 1: FH		Type 2: EO		Type 3: GS
Design	*Analyses*	*Design*	*Analyses*	*Analyses*
1	0	0	4	10
3	1	3	9	2
1	0	3	8	0
0	0	1	6	5
3	0	0	4	0
2	1	0	3	0
1	0	0	3	1
0	0	1	1	2
1	0	0	2	0
0	0	0	2	1
0	1	0	1	0
0	1	0	1	0
0	0	0	1	0
0	0	0	1	0

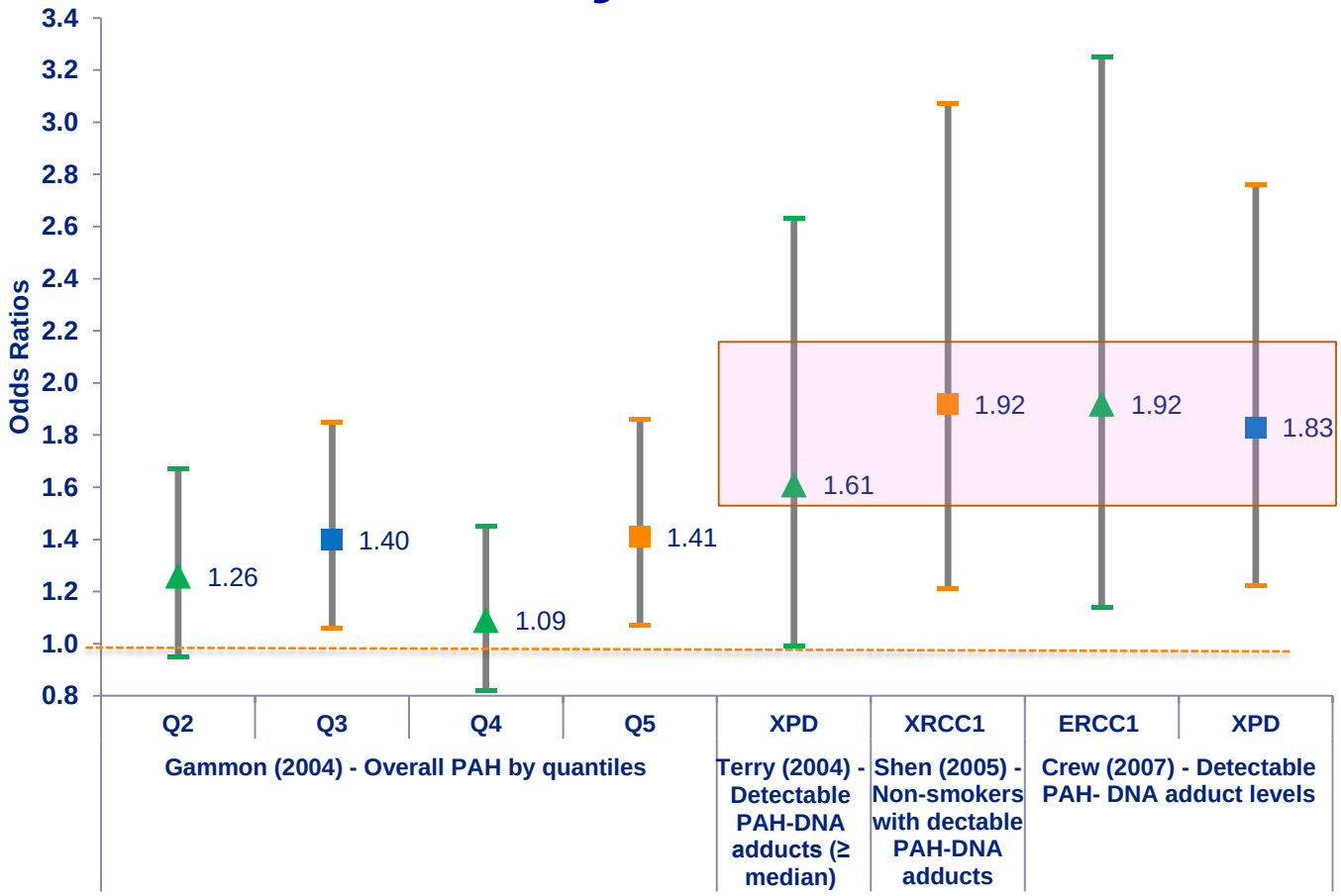
tic susceptibility
several publications examined more than one exposure or fell into more

ional PAH surrogates, ambient fine-particulate matter ($PM_{2.5}$ and PM_{10}) and nitrogen dioxide (NO_2), indoor heating and cooking, vehicular exhaust

Number of publications: 1 | 2 | 3-4 | 5-7 | 8-10

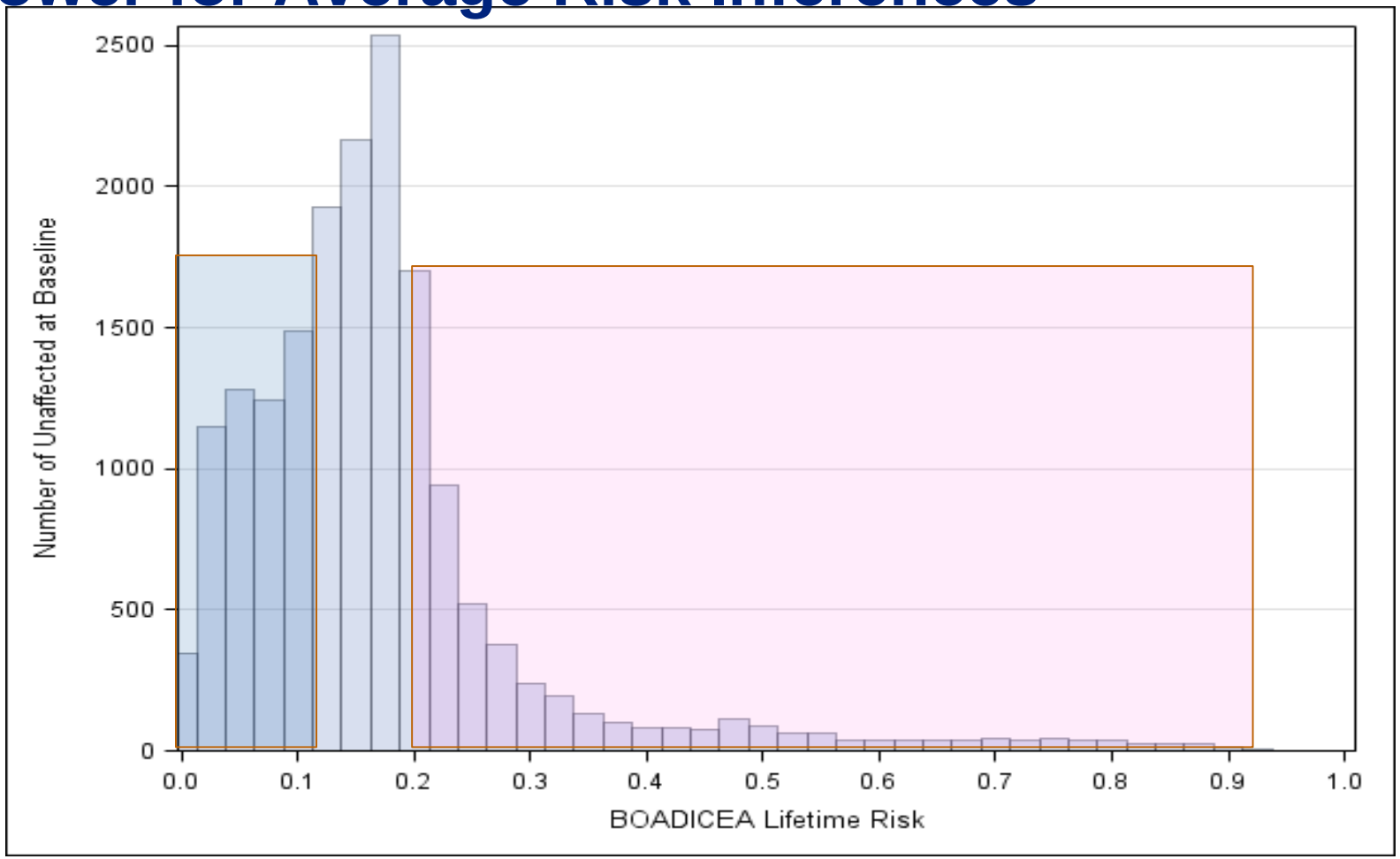
PAH as an Example of why Targeted Approaches can inform Population-wide Health

PAH-DNA Adducts and Breast Cancer Risk in a Population-Based Study



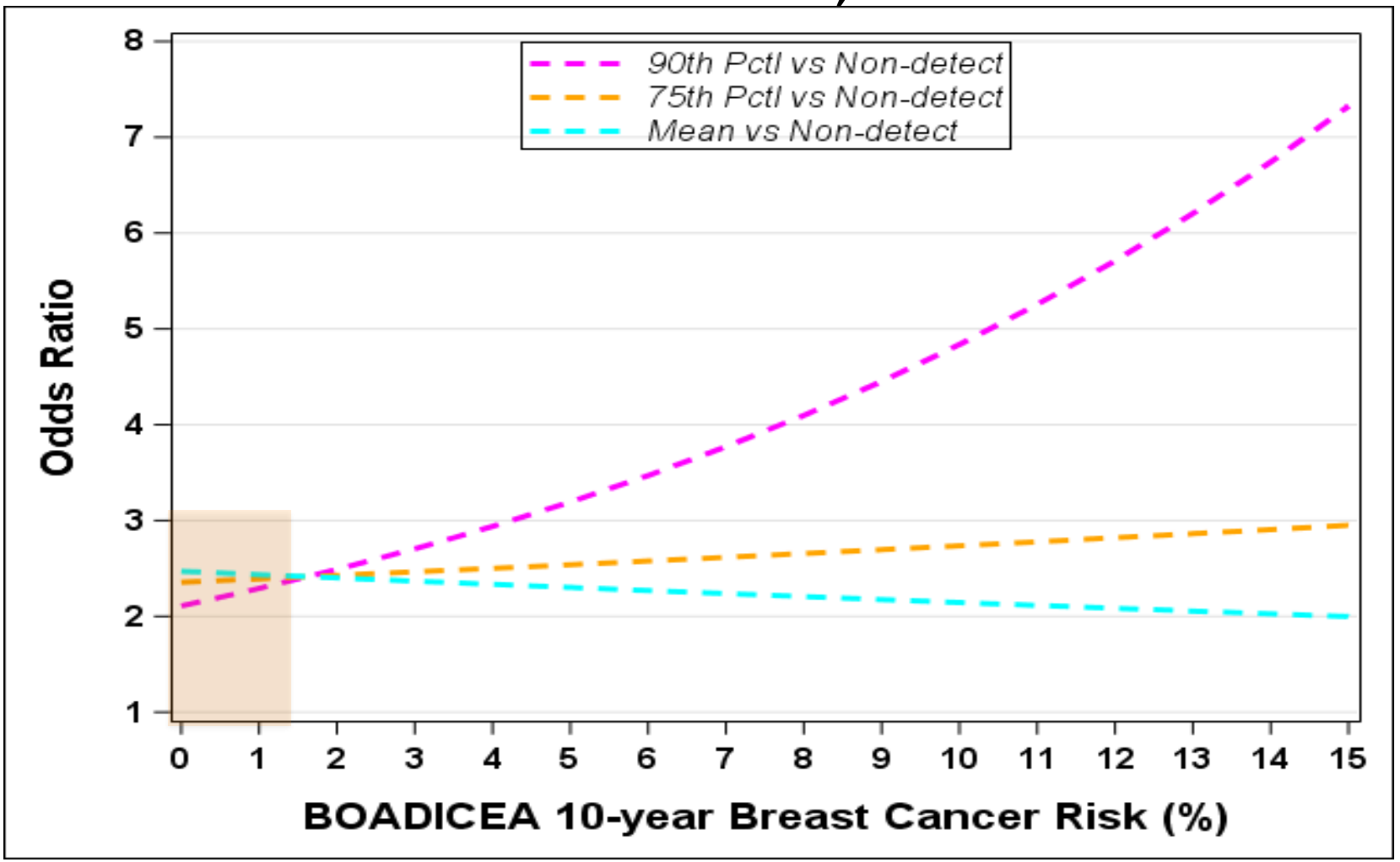
Gammon MD, et al., Arch Environ Health, 2004;
Terry MB et al., Cancer Epidemiol Biomarkers Prev., 2004;
Shen J et al., Cancer Epidemiol Biomarkers Prev., 2005;
Crew KD et al., Cancer Epidemiol Biomarkers Prev., 2007.

Family-based Cohorts Have Power at the Tail and Power for Average Risk Inferences



Prospective Family Study Cohort (PROF-SC)

Example of GXE: Increase in breast cancer risk from PAH by absolute risk of breast cancer, New York site of BCFR



BOADICEA 10-year Breast Cancer Risk	3.4%	10%
Mean vs Non-detect, OR (95% CI)	2.35 (1.13, 4.91)	2.14 (1.00, 4.60)
75th % vs Non-detect, OR (95% CI)	2.48 (1.14, 5.41)	2.74 (1.18, 6.36)
90th % vs Non-detect, OR (95% CI)	2.80 (1.05, 7.46)	4.84 (1.41, 16.5)

Shen J et al., British Journal of Cancer 2017

Most empirical evidence relatively modest

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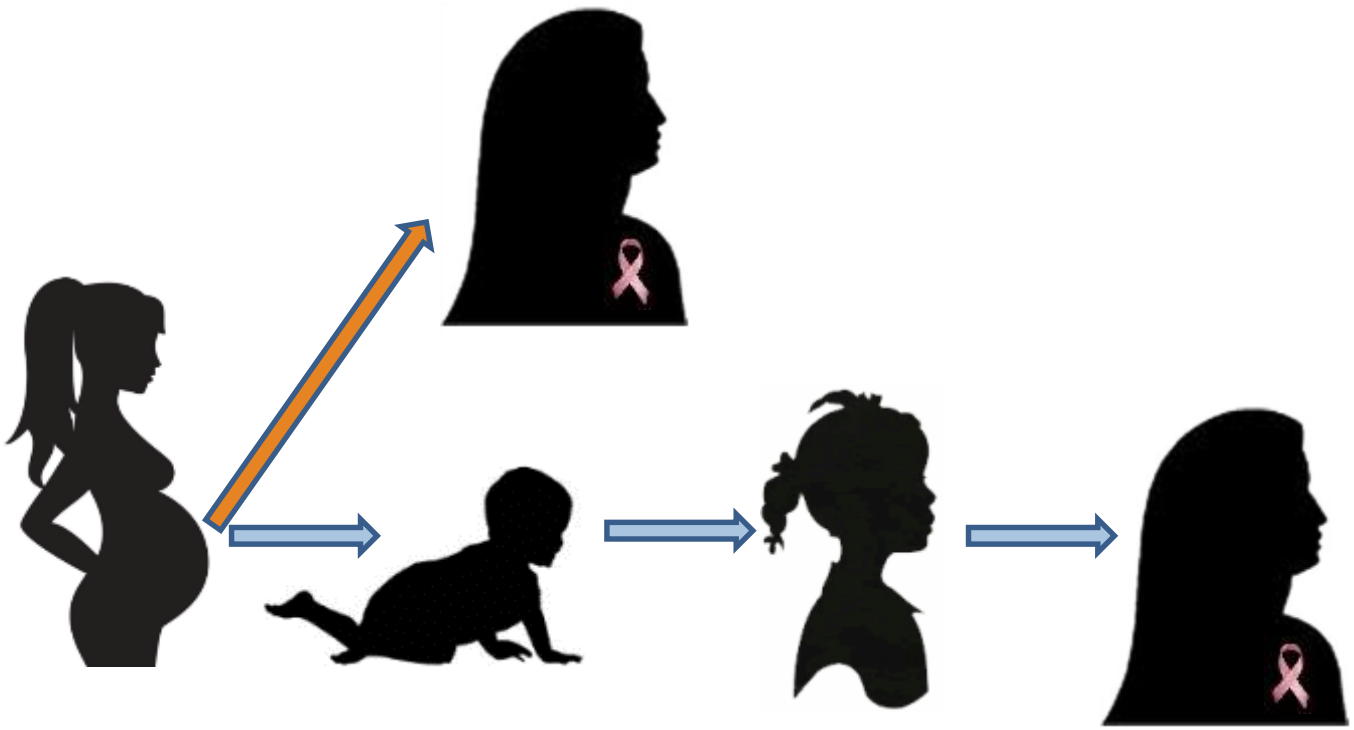
Intergenerational Health



PEDIGREE: Prenatal Environmental Determinants of Inter-Generational Risk

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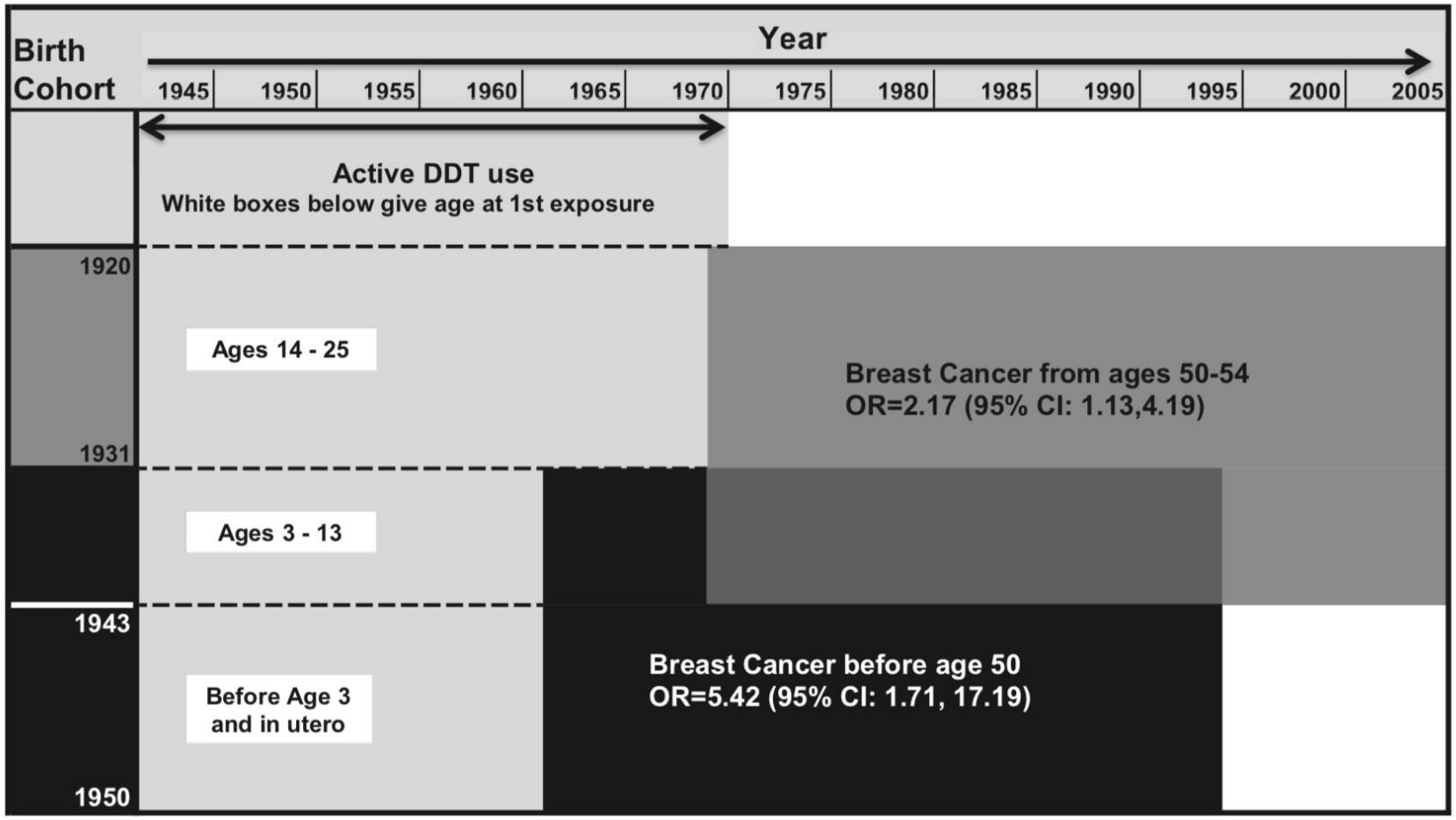
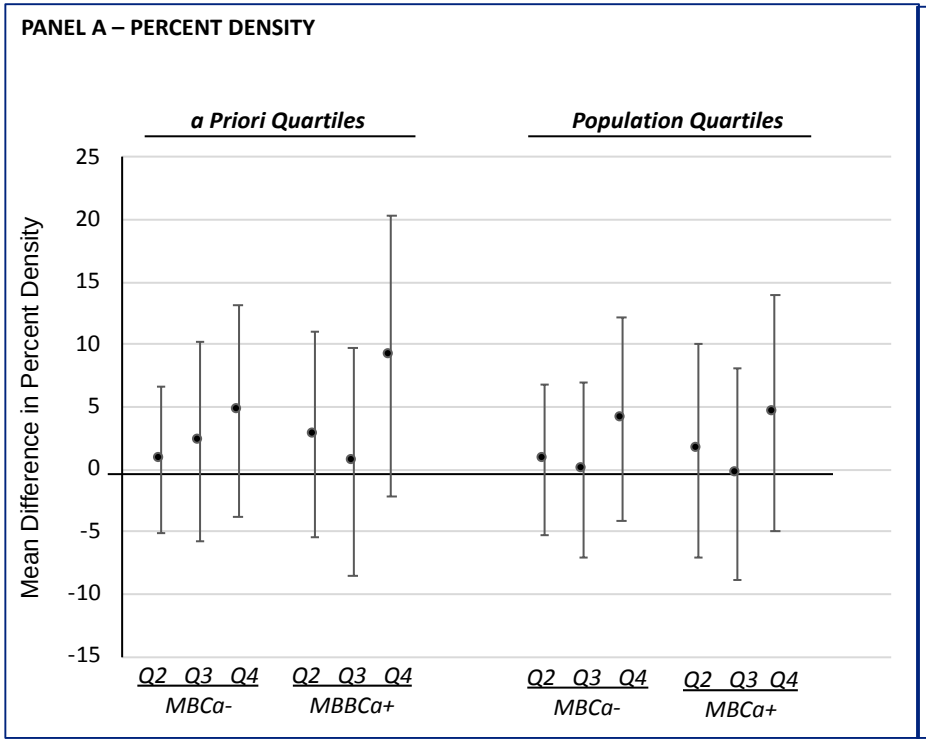
Cohn et al, JNCI 2019; Krigbaum et al, J Dev Orig Health Dis 2017;
Cohn et al, Breast Cancer Res Treat 2012;

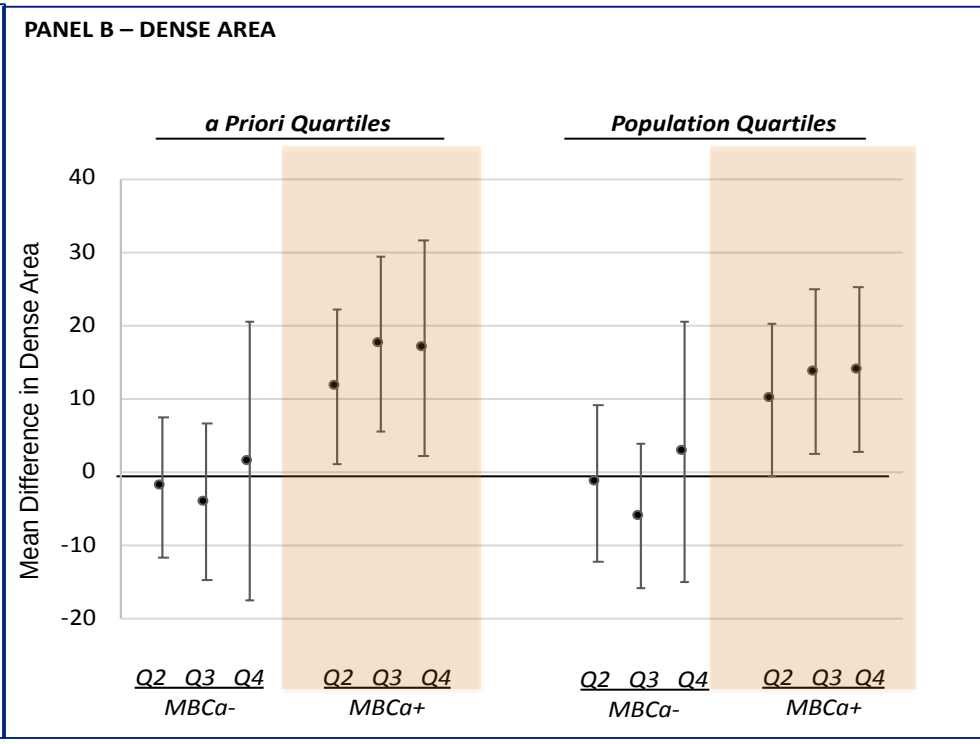
U01ES019471

Integration of WOS and Susceptibility

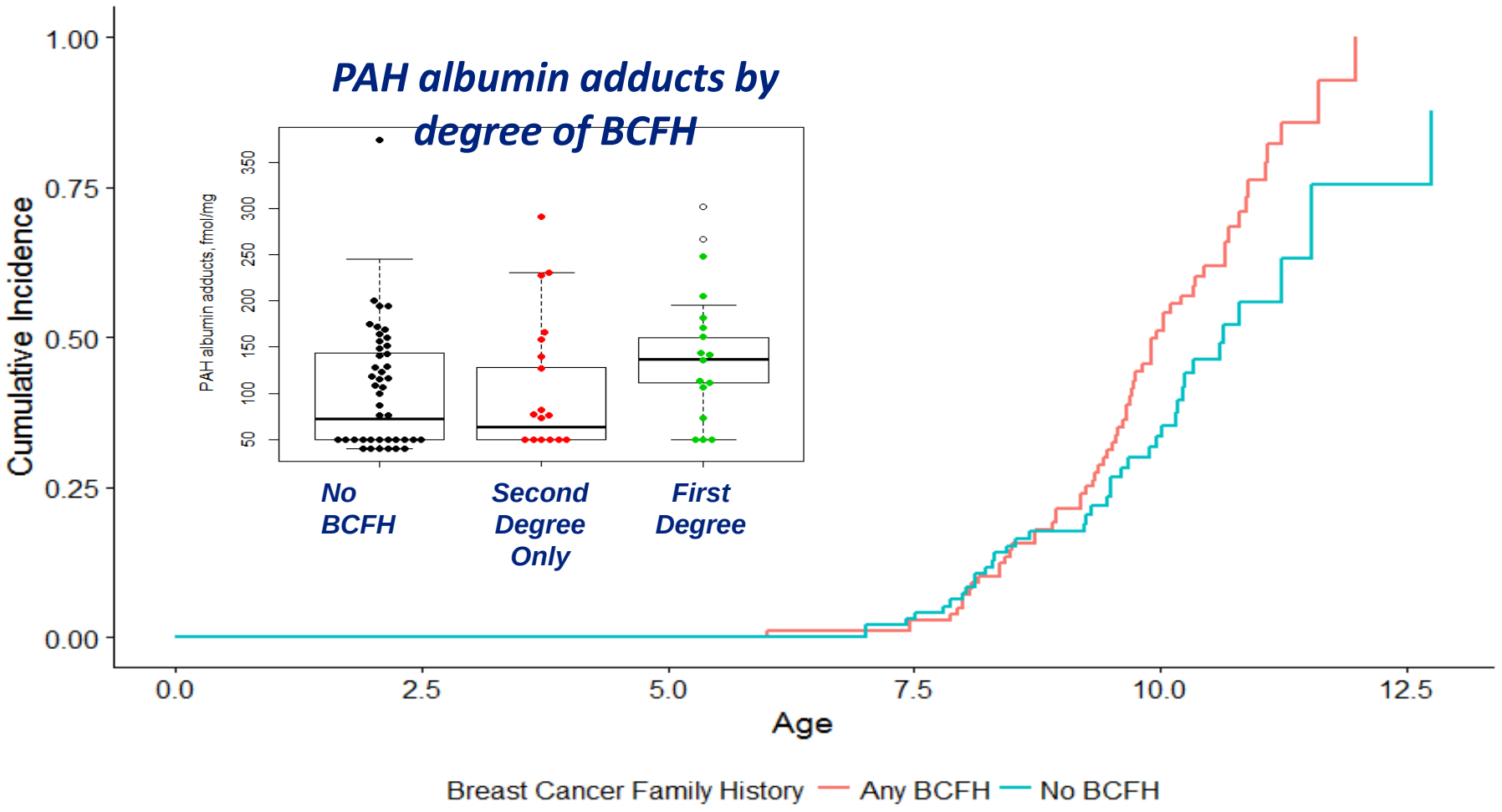


o,p'-DDT Exposure and Daughter's Mammographic Breast Density by Mothers Breast Cancer Status, PEDIGREE





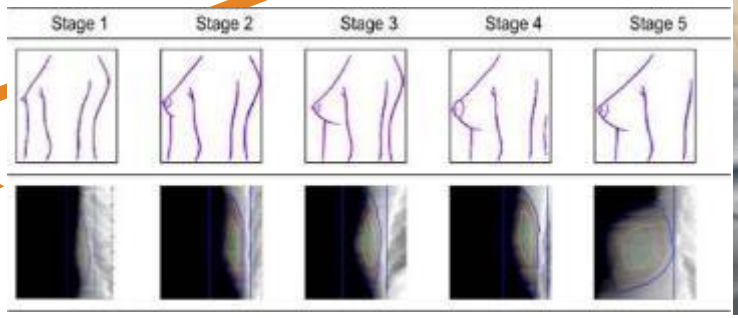
Non-Overweight Girls (BMI < 85th) with BCFH have earlier breast development

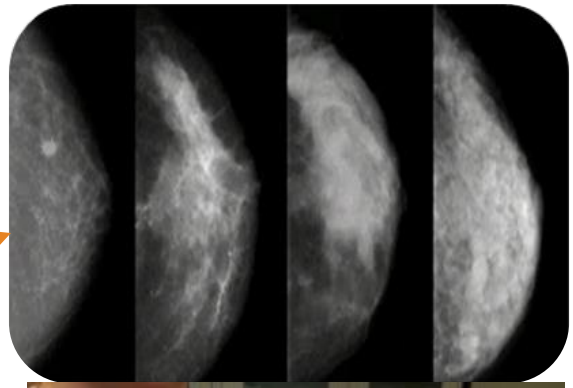


Terry MB et al Breast Cancer Research 2017
Lilge L, Terry MB et al. Breast Cancer Research, 2017

Mother-Child Cohorts: BCERP

Adolescent breast development in daughters using OS





NIEHS grant U01ES026122 (2014-2019)

Measurement of PAH Exposure in the CCCEH Cohort

Prenatal Questionnaire → **Area and residential monitoring and GIS-PAH** → **Personal Exposure-PAH, etc.** → **Internal Dose** → **Biologically effective dose**

Backpack worn 2 consecutive days during 3rd trimester.

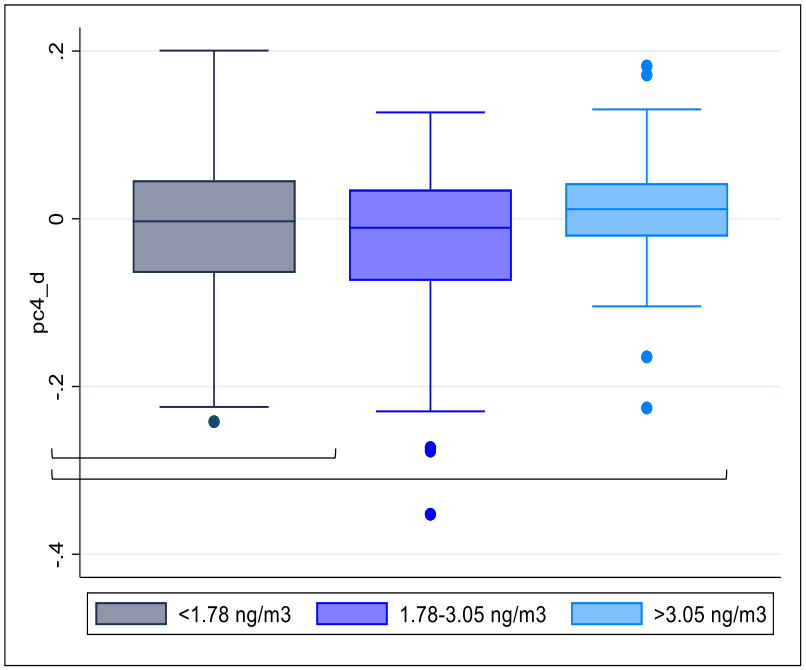
Urinary PAH metabolites

PAH-DNA adducts

Maternal blood sample
Cord blood sample

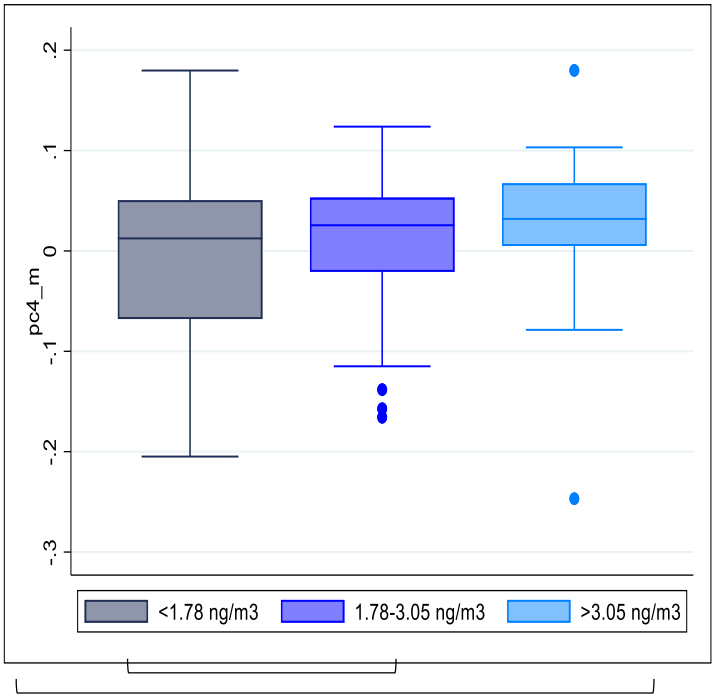
Exposure to ambient PAH during the prenatal or pregnancy period and breast tissue composition in daughters and mothers

Daughters (n=164), PC4



β = -0.05 (p=0.79) **β = 0.40** (p=0.04)

Mothers (n=159), PC4



β = 0.24 (p=0.22) **β = 0.44** (p=0.03)

Models adjusted for ethnicity, age and BMI at OS measurement

Summary and Implications

Limited but growing evidence

1) for all WOS, studies suggest stronger and more consistent associations than outside WOS

2) for higher risk individuals suggest stronger and more consistent associations than cohorts of average risk

Family-based cohorts are an efficient design to study environmental factors

Just like with genes, results still relevant to those without a family history

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