PRECISION PREVENTION: GENE & ENVIRONMENT INTERACTIONS: PAHS AND THE BREAST CANCER FAMILY COHORT

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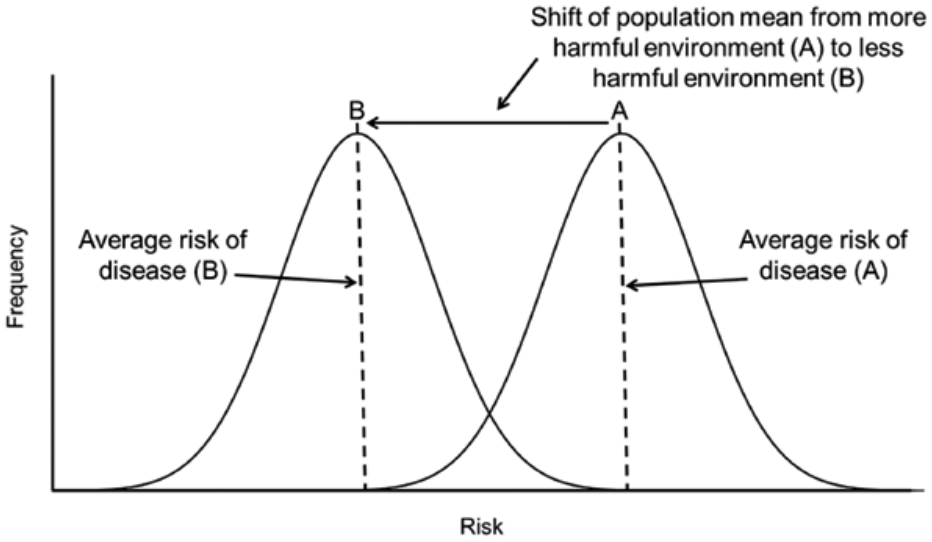
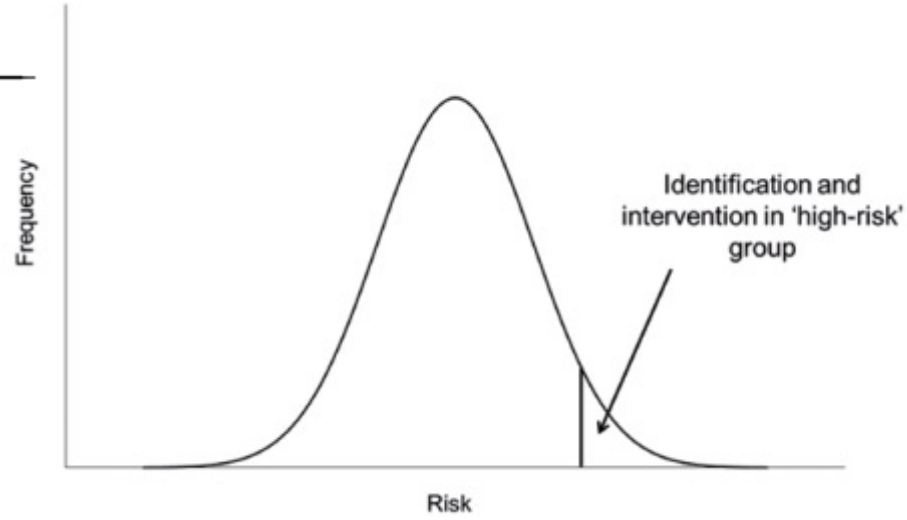
I have no conflicts of interest to declare

Population-wide approaches for prevention



Population-based

vs. Non-population based approaches for discovery



High-risk

Cancer Genes vs. Environmental Risk Factors

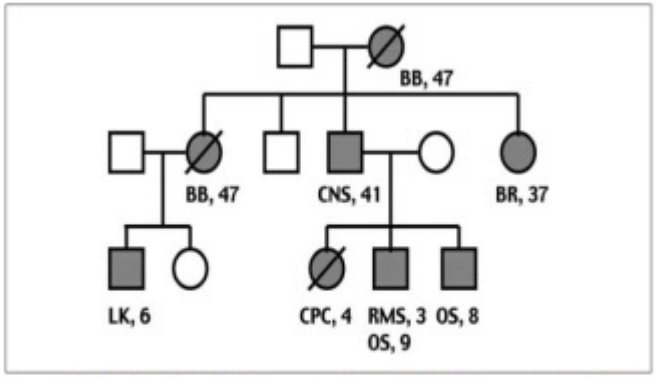
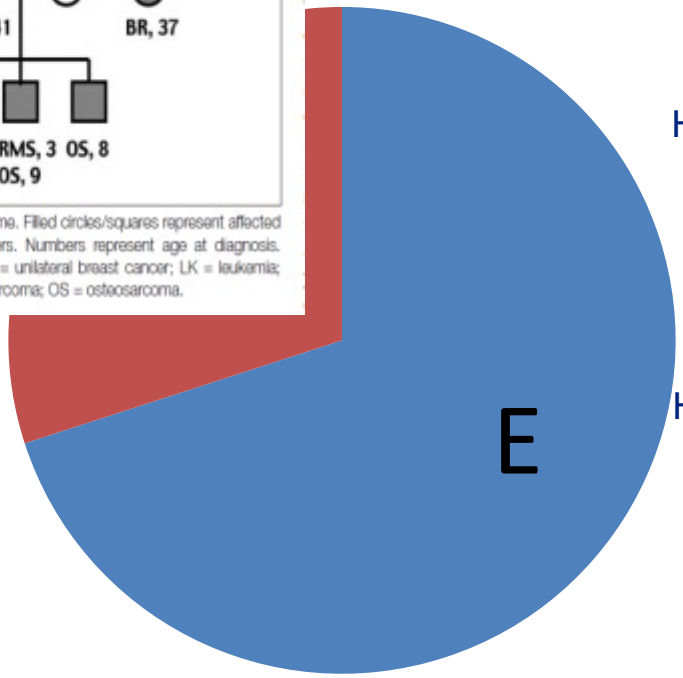


Figure 1. Pedigree of a family with Li-Fraumeni syndrome. Filled circles/squares represent affected members; slashes represent deceased family members. Numbers represent age at diagnosis. BB = bilateral breast cancer; CNS = brain tumor; BR = unilateral breast cancer; LK = leukemia; CPC = choroid plexus carcinoma; RMS = rhabdomyosarcoma; OS = osteosarcoma.

P53
Rb
MLH1
MSH2
BRCA1
BRCA2
APC

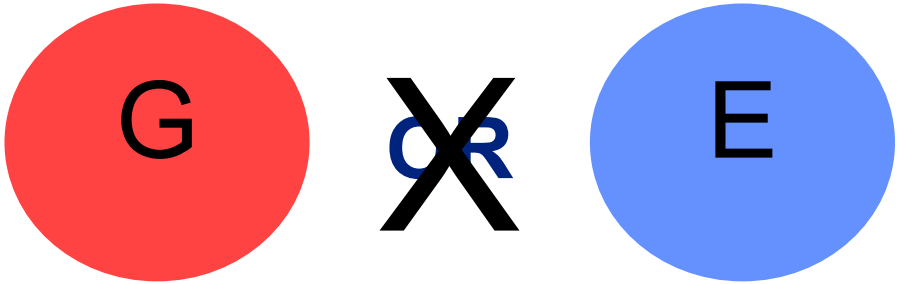
and many others…

High and intermediate penetrant genes first discovered in family studies



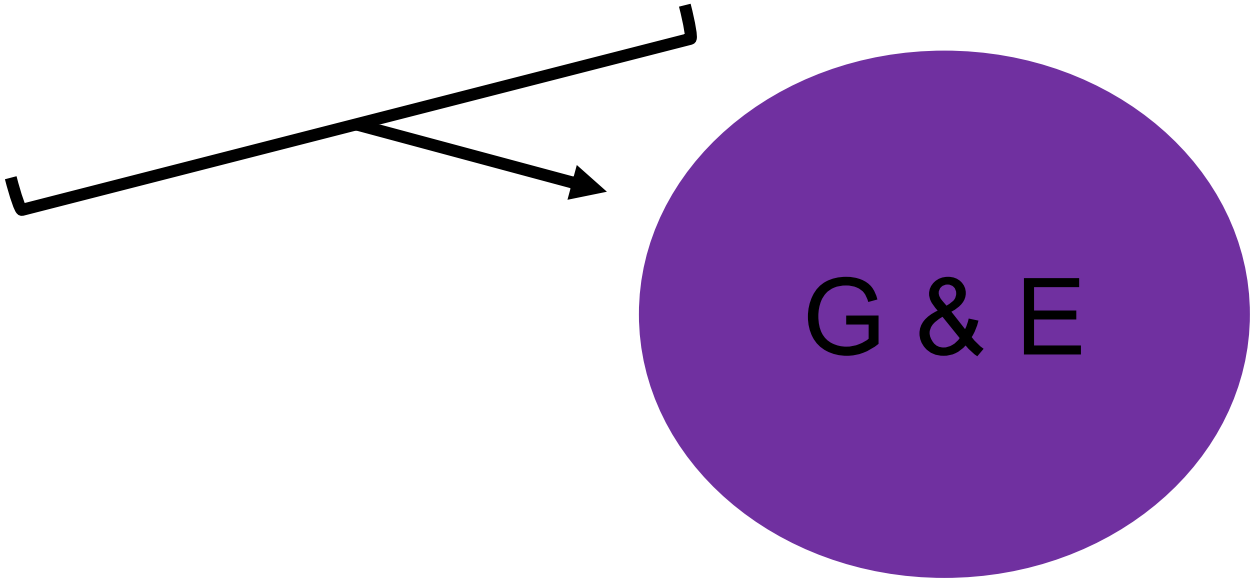
Risk Factor	Cancer Site
Tobacco	Lung and others
Asbestos	Lung
H. Pylori Infection	Gastric Cancer
Human Papillomavirus (HPV) Infection	Cervical Cancer,Anal, Head&Neck
Vinyl Chloride	Liver
Hepatitis B and C Infection	Liver
Maternal Diethylstilbestrol (DES) Use	Vaginal Adenocarcinoma
Ionizing Radiation	Leukemia
Alcohol	Liver, Head & Neck, Colon, Breast, others

Genes (G) AND the Environment (E)



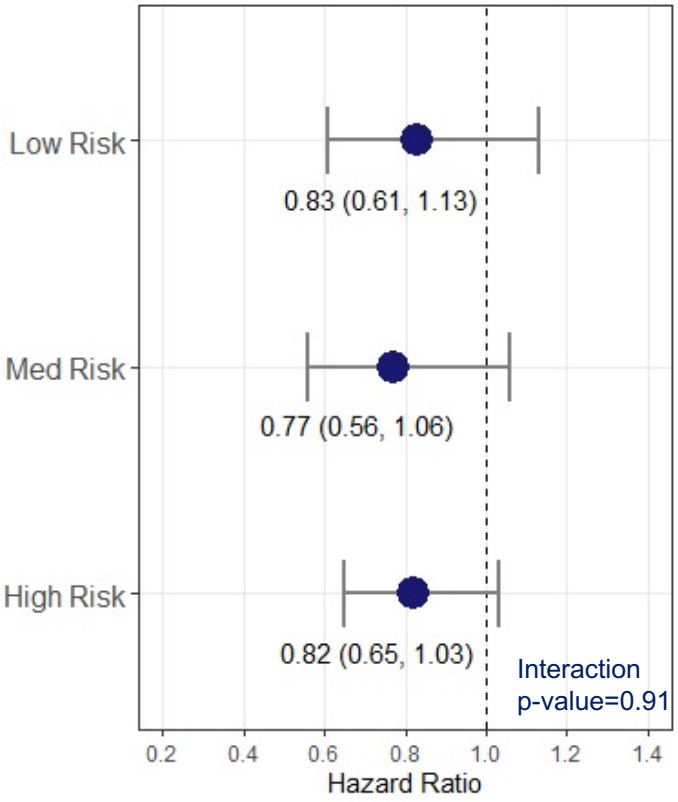
Environmental factors may be even more important for those with higher susceptibility

Genes that have been discovered using family studies are important for people without a family history

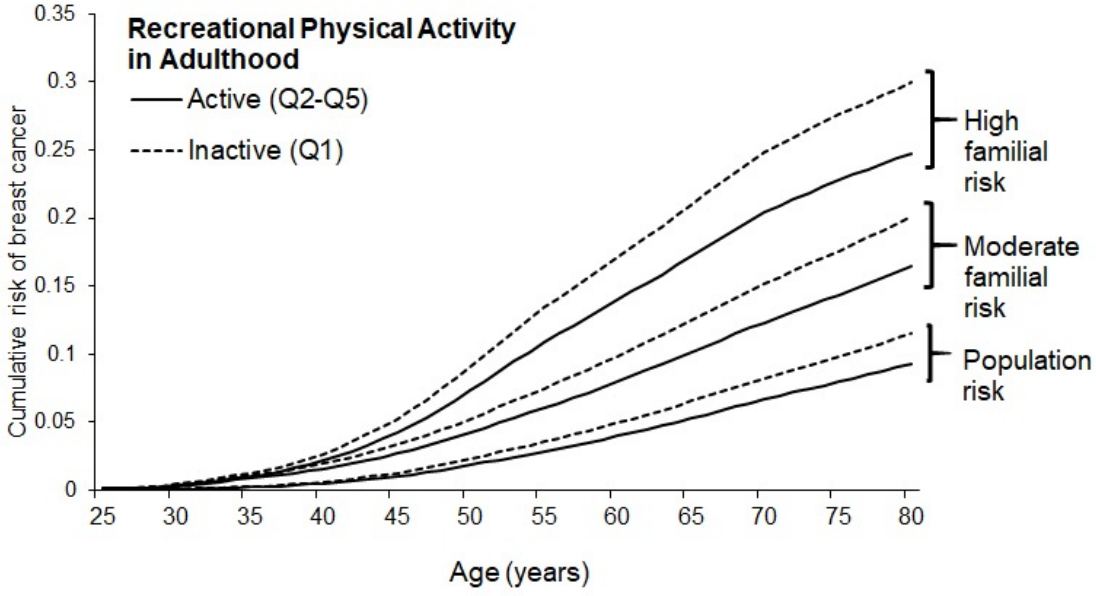


Modifiable risk factors are important for individuals with higher underlying susceptibility

Even when there is no effect modification between physical activity and BC risk on the multiplicative scale

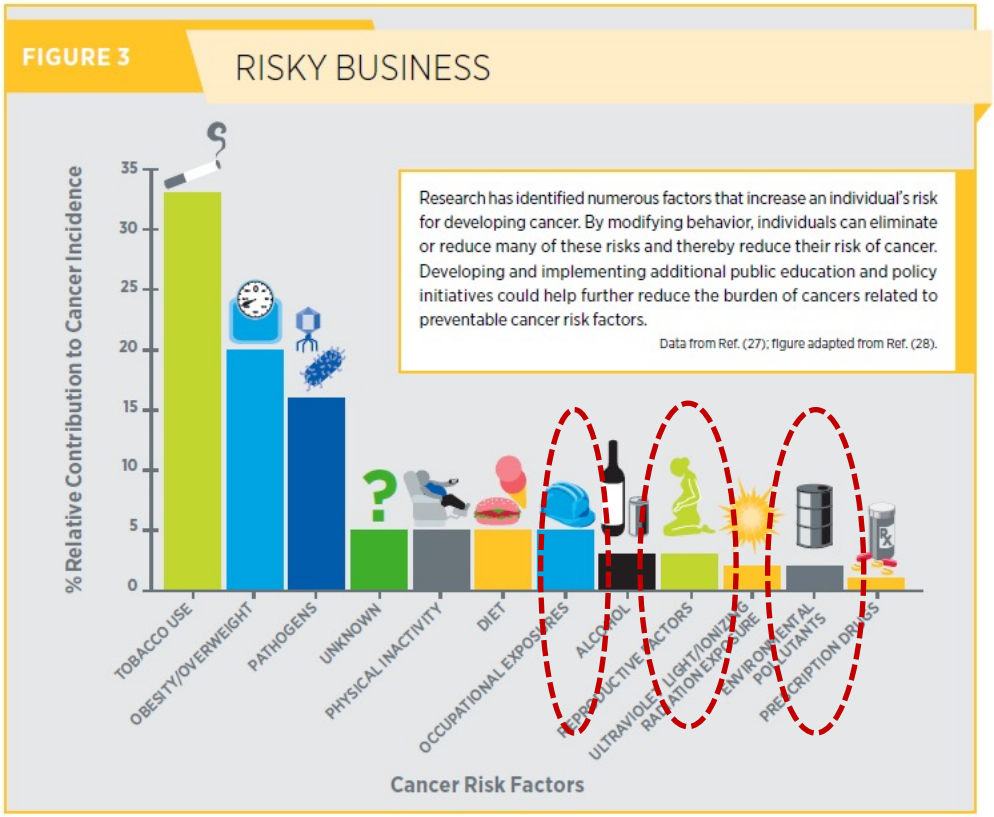


Larger absolute risk reduction for those at higher risk

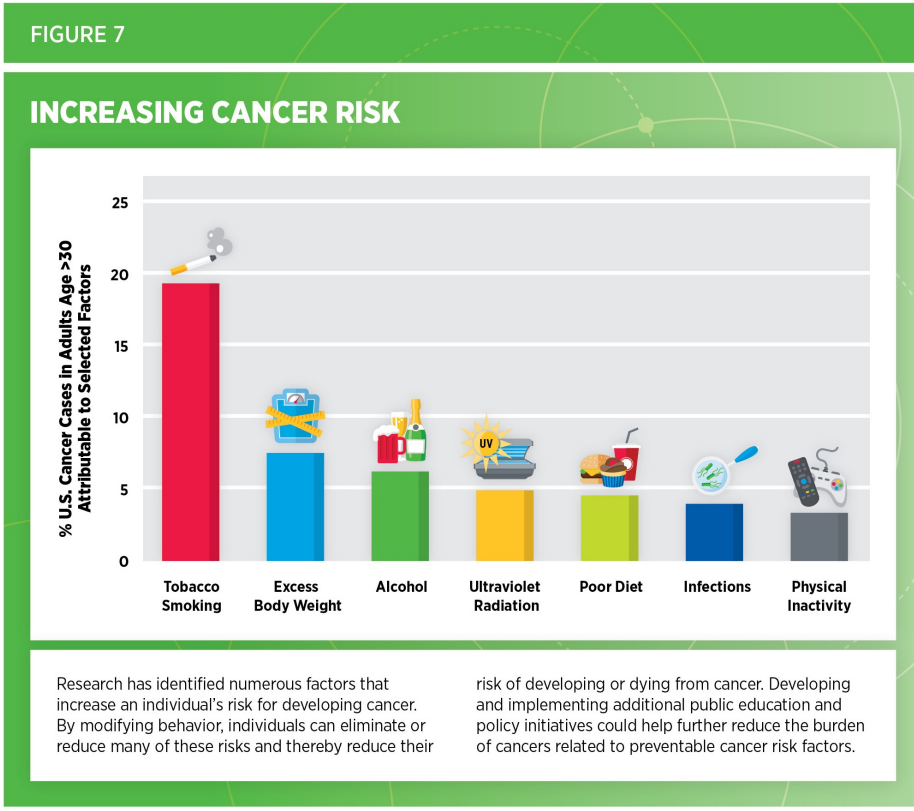


Kehm RD et al. Cancer Research 2020

And YET, what happens when risk is communicated and attributed?



Source: AACR Cancer Progress Report 2016, p24.



American Association for Cancer Research (AACR) Cancer Progress Report 2021

All cancers combined, single risk factors when we are exposed to many at the same time , focus on individual risk modification

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We know that cancer is related to whether you smoke and your diet

But I don't smoke and I eat well, what about the environment?

Key Challenges

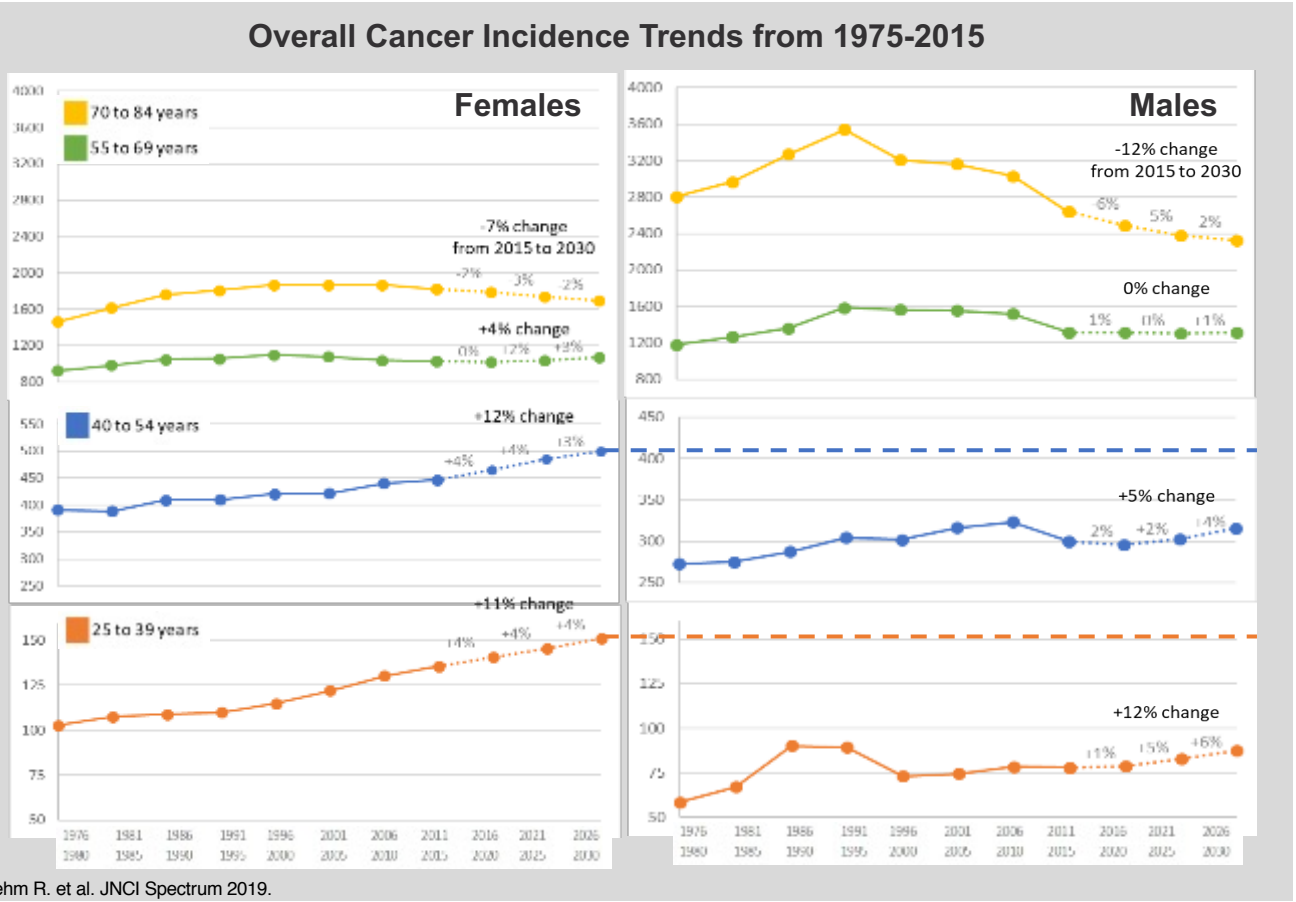
1) **Overall cancer attribution clouds the heterogeneity across cancers in causes**

   e.g., World Health Organization estimates 25% of cancers of the trachea, bronchus and lung, as well as 63% of mesothelioma, are attributed to occupational environmental exposures

2) **Attribution is also very much related to how well we can measure things**

   e.g., Smoking is much easier to measure (e.g. can be queried by questionnaire) than environmental and chemical exposures (which often require expensive assays using biospecimens)

U.S. Cancer Incidence Trends



Kehm R. et al. JNCI Spectrum 2019.

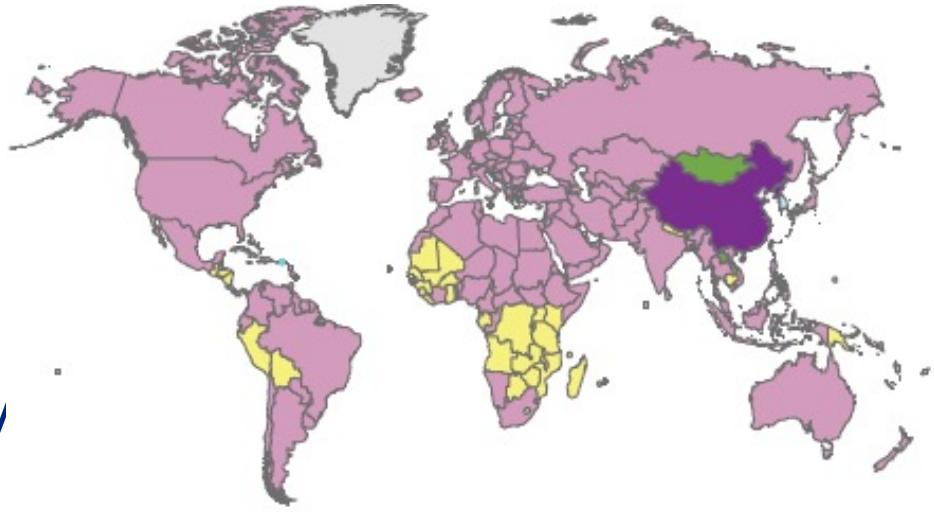
Increasing incidence NOT driven by G

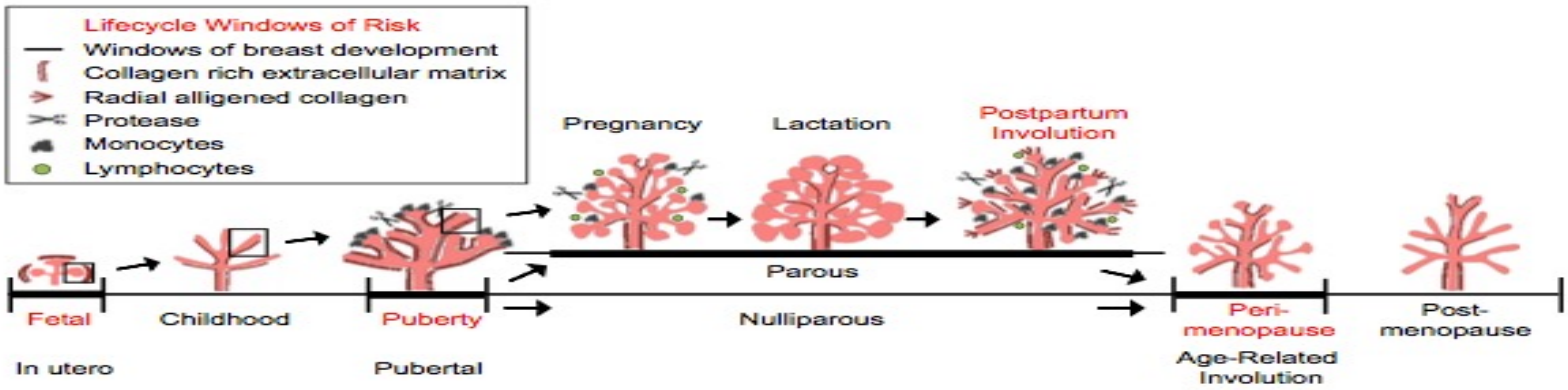
Driven by secular changes in E and GXE

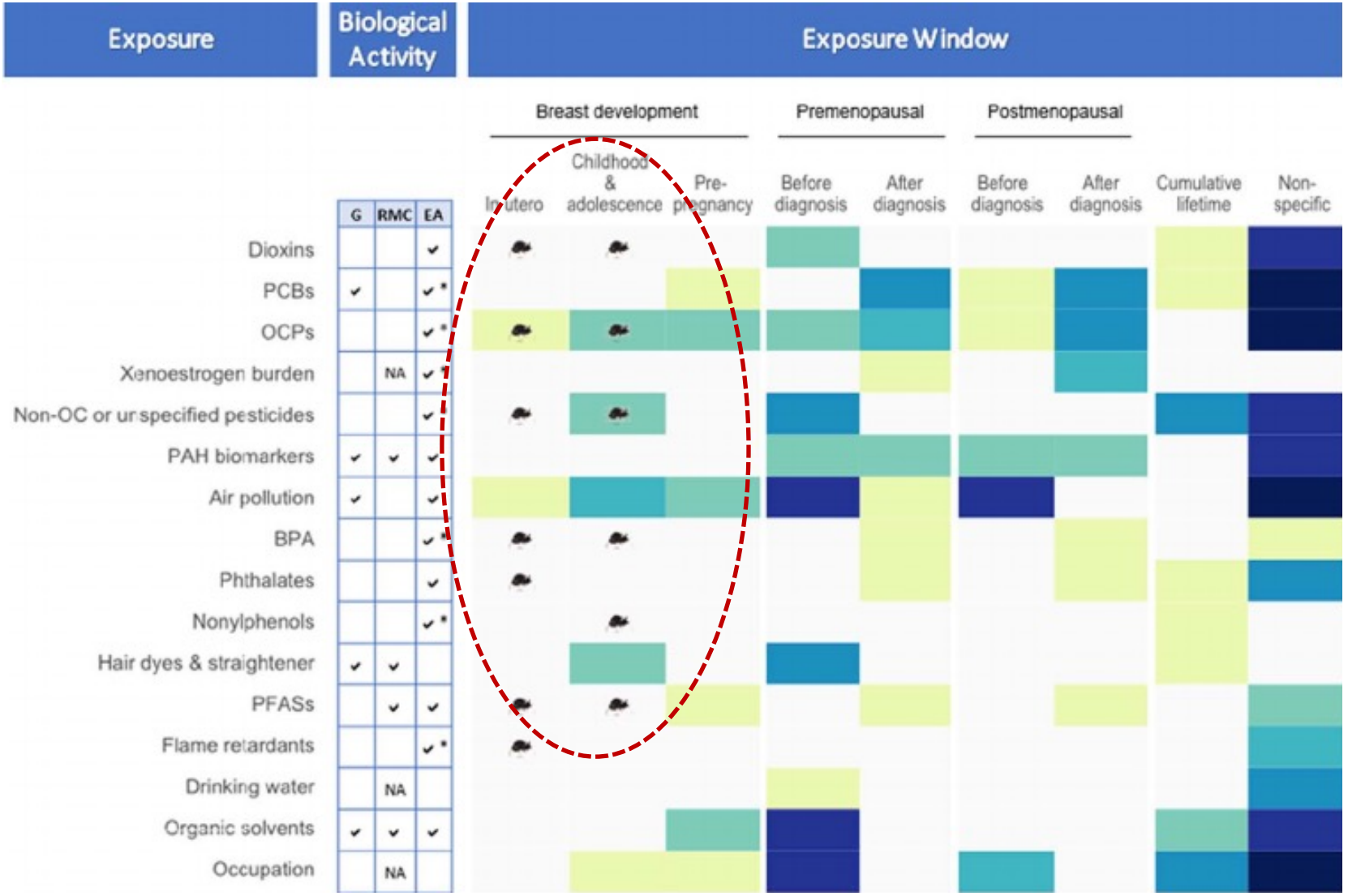
The Case of Breast Cancer

1) Most common cancer globally in women

2) Breast cancer risk is increased during key windows of susceptibility (WOS)



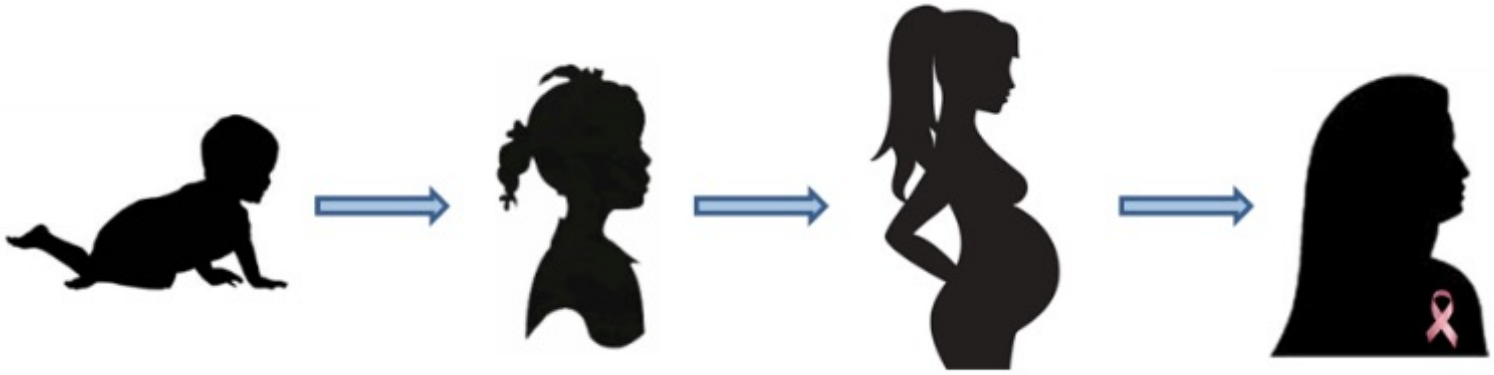




N=158, 2006-2016, 11% specific to WOS

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

When we look at studies specific to Windows of Susceptibility (WOS) data are much more consistent



- ***Regional total suspended particulates***
- ***Maternal o,p'-DDT***
- ***p,p'-DDT metabolites in serum***
- ***during pregnancy including 10 PFCA, 5 PFSA, and PFOSA***
- ***Serum PCB during early postpartum***
- ***Urinary cadmium***
- ***Dietary cadmium***

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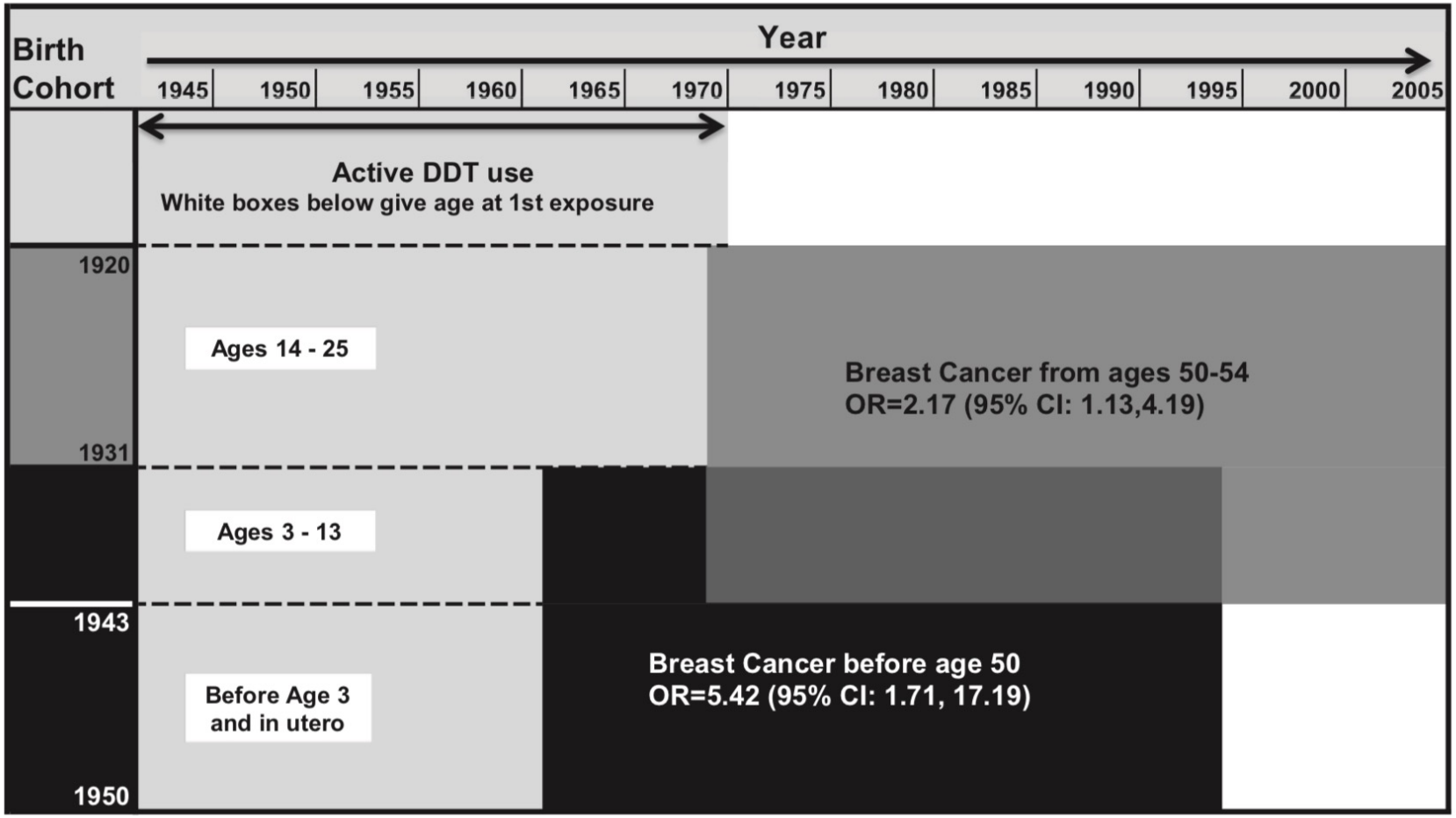
Martinson et al. Exp Cell Res. 2013

BCERP Framework Paper Breast Cancer Research 2019.

Windows of Susceptibility (WOS)



Cohn BA, Cirillo PM, Terry MB JNCI 2019

Studies of Environmental Exposures and Breast Cancer in Enriched Cohorts based on Family history (Type 1), Early onset breast cancer (Type 2), or GXE (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
ıst

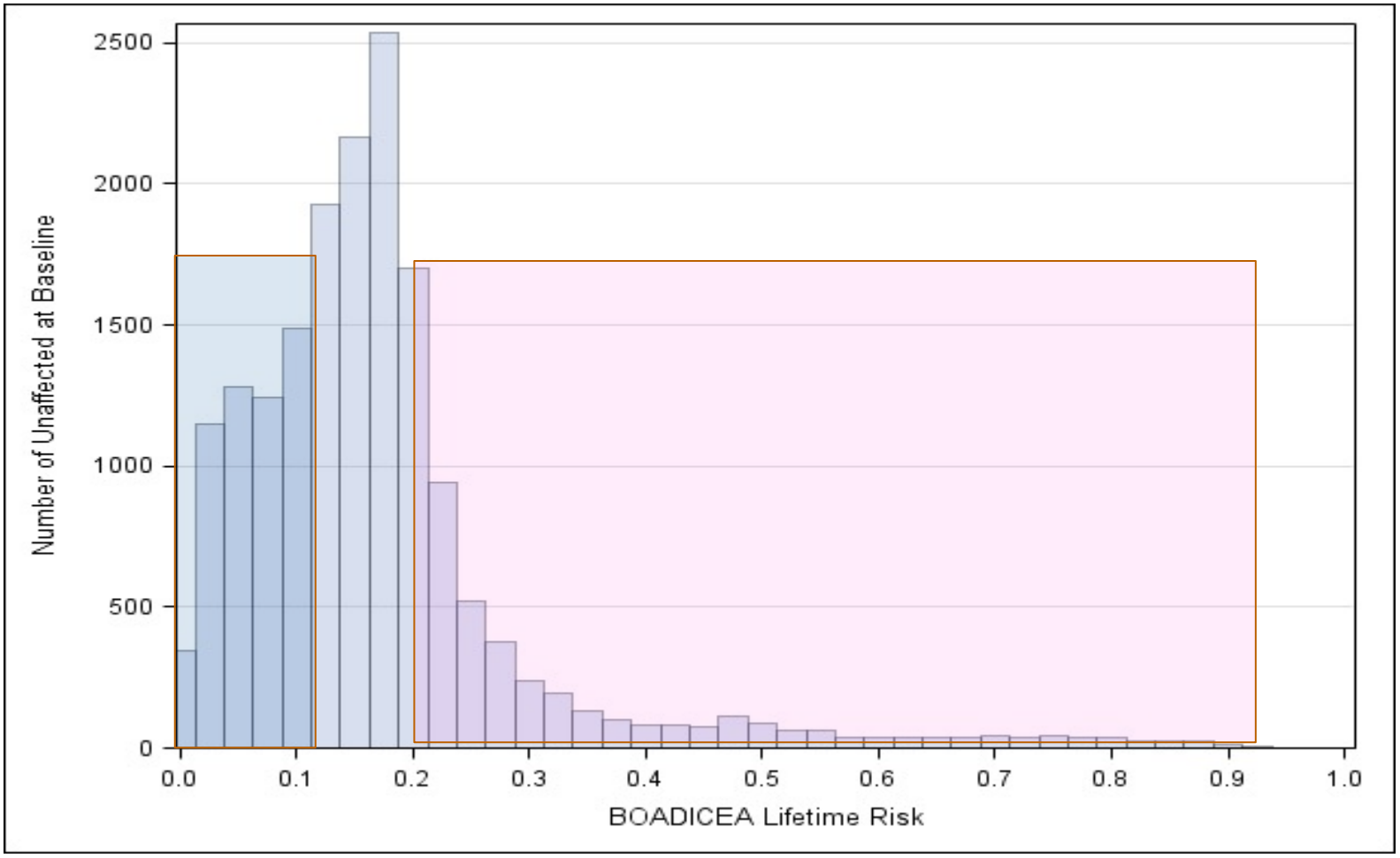
1	2	3-4	5-7	8-10

Zeinomar N et al Environ Res. 2020.

Key Considerations:

1) Most cancer happens in older adults
2) Population-based studies will therefore include more individuals whose risk of cancer is based on exposures as well as endogenous related aging processes
3) Enriched cohorts have individuals at much higher absolute risk to increase statistical power for testing GXE – robust design for testing GXE

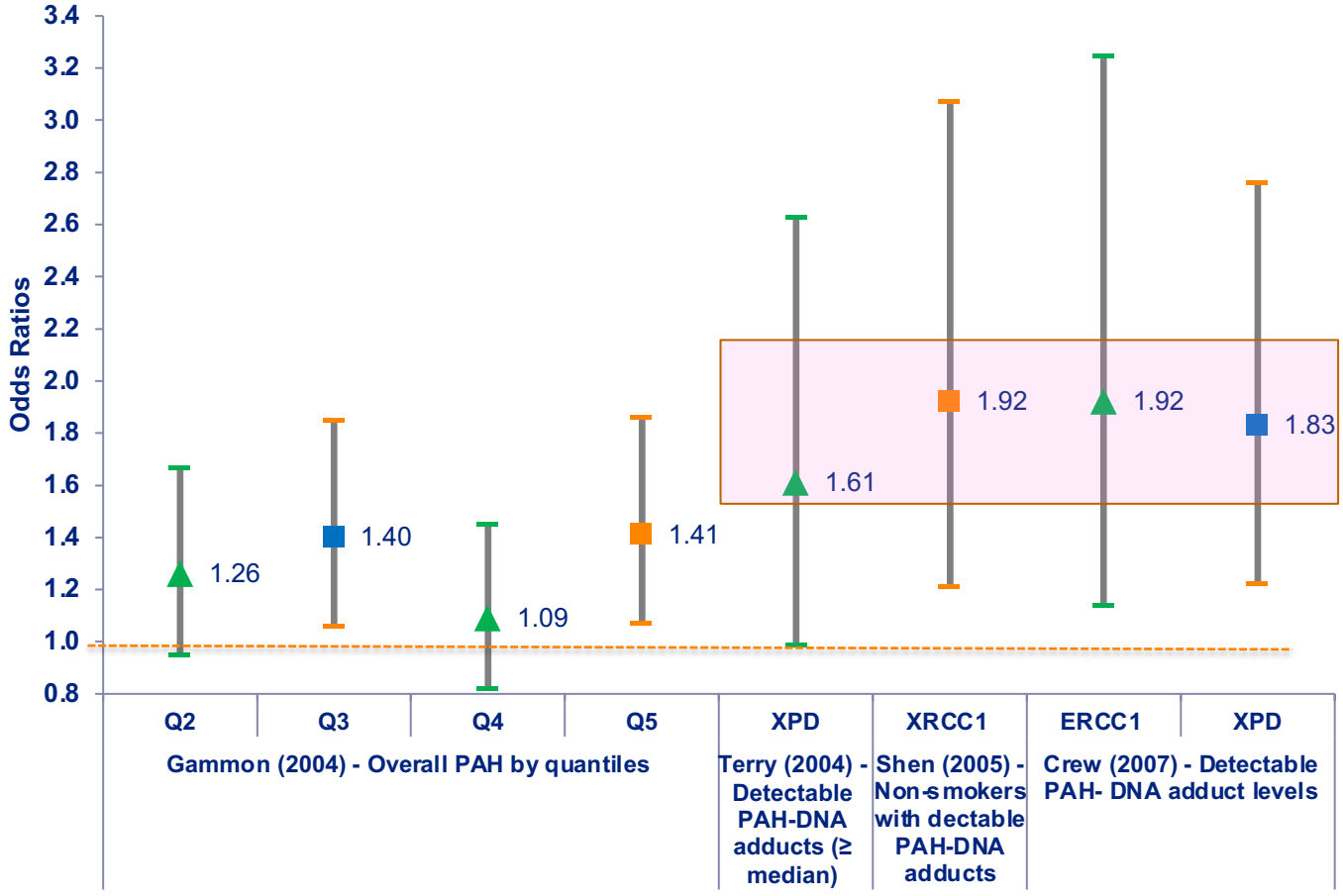
Why enriched cohorts based on family history may shed light on environmental exposures



Prospective Family Study Cohort (PROF-SC)

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



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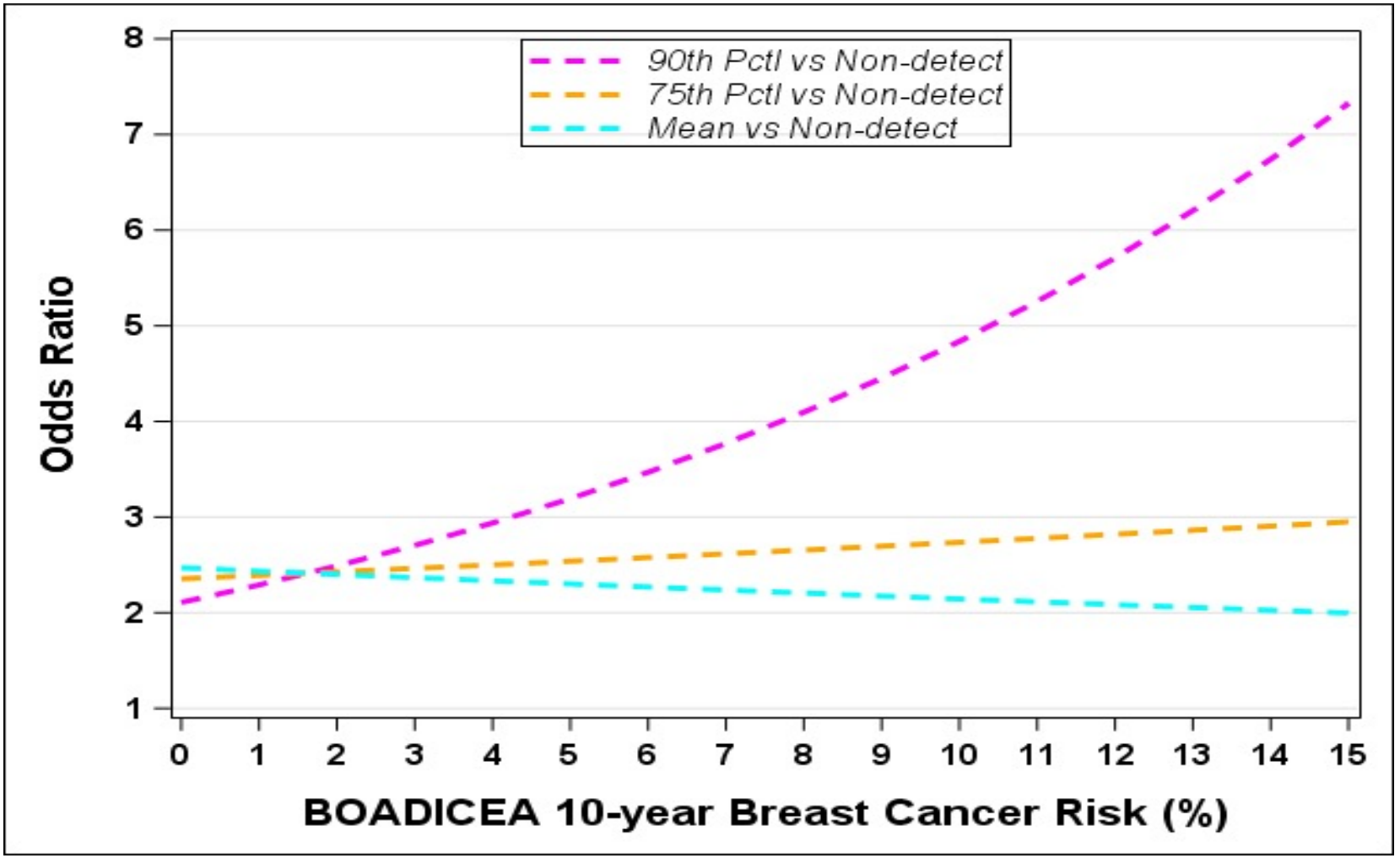
Gammon MD, et al., Arch Environ Health, 2004;
Terry MB et al., Cancer Epidemiol Biomarkers Prev., 2004;
Shen J et al., Cancer Epidemiol Biomarkers Prev., 2005;
Crew KD et al., Cancer Epidemiol Biomarkers Prev., 2007.

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

Do you think that chemicals in the environment can increase my breast cancer risk?

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Walker DAH and Terry MB. Is it 'cancer prevention' or 'risk reduction'? #Wordsmatter. Cancer Causes Control 2021 32(9):919-922.

Summary and Implications

1) *Not G or E, but G & E*
2) *Need to consider the impact of underlying susceptibility, particularly for common exposures*
3) *In the case of environmental exposures and breast cancer*
    a) *For all windows of susceptibility, studies suggest stronger and more consistent associations than outside of WOS*
    b) *For higher risk individuals, studies suggest stronger and more consistent associations than cohorts of average risk*

4) Just like with genes, results from enriched cohorts still relevant to those without a family history

BREAST CANCER FAMILY REGISTRY

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