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?


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

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

Windows of Susceptibility (WOS)

Columbia

Michigan

UMASS

City of Hope

UCLA/Chile

Columbia

Georgetown

Life cycle windows of risk:
- Windows of breast development
- Collagen rich extracellular matrix
- Radial alligned collagen
- Protease
- Monocytes
- Lymphocytes

Pregnancy → Lactation → Postpartum Involution

Fetal → Childhood → Puberty → Parous → Nulliparous

In utero → Pubertal → Parous → Peri-menopause → Post-menopause

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
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
# 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

Design Analyses

<table>
<thead>
<tr>
<th>Type 1: FH</th>
<th>Type 2: EO</th>
<th>Type 3: GS</th>
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ic susceptibility
several publications examined more than one exposure or fell into more

40% PAH surrogates, ambient fine-particulate matter (PM$_{2.5}$ and PM$_{10}$) and

nitrogen dioxide (NO$_2$), indoor heating and cooking, vehicular exhaust
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**

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

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

Cohn et al, JNCI 2019; Krigbaum et al, J Dev Orig Health Dis 2017;
Cohn et al, Breast Cancer Res Treat 2012;
Integration of WOS and Susceptibility

- Active DDT use
- White boxes below give age at 1st exposure

- Breast Cancer from ages 50-54
  OR=2.17 (95% CI: 1.13,4.19)

- Breast Cancer before age 50
  OR=5.42 (95% CI: 1.71, 17.19)

Cohn BA, Cirillo PM, Terry MB JNCI 2019
o,p’-DDT Exposure and Daughter’s Mammographic Breast Density by Mothers Breast Cancer Status, PEDIGREE

**PANEL A – PERCENT DENSITY**

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<th>a Priori Quartiles</th>
<th>Population Quartiles</th>
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**PANEL B – DENSE AREA**

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<td>Mean Difference in Dense Area</td>
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*McDonald JA et al, 2019 Reproductive Toxicology*
Non-Overweight Girls (BMI < 85th) with BCFH have earlier breast development

PAH albumin adducts by degree of BCFH

Breast Cancer Family History
- Any BCFH
- No BCFH

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

- Urinary PAH metabolites
- PAH-DNA adducts
- Backpack worn 2 consecutive days during 3rd trimester.
- 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

- $\beta = -0.05$ (p=0.79)
- $\beta = 0.40$ (p=0.04)

Models adjusted for ethnicity, age and BMI at OS measurement

Mothers (n=159), PC4

- $\beta = 0.24$ (p=0.22)
- $\beta = 0.44$ (p=0.03)
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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