Effects of Environmental Chemicals in Pregnancy on Cancer in Two Generations

Case Study: DDT and Breast Cancer

Barbara Cohn, PhD
Child Health and Development Studies
Public Health Institute
OUTLINE

• Why DDT case study
• Why multi-generational studies
• Child Health and Development Studies
• What we found for mothers and their daughters
• Examples and promise of big data
• Relation to disparities
• Next steps
Alive 1945-2020? You are Exposed to DDT

Insecticide
($p,p'$-DDT)

Contaminant
($o,p'$-DDT)

Metabolite
($p,p'$-DDE)
Exposures to pregnant women impact three generations simultaneously

Adapted from Perera F, Herbstman J, Reproductive Toxicology PMID: 21256208
• Initiated in 1959
• Enrolled ~ 20,000 pregnancies by 1967
• Partnership with Kaiser Foundation Health Plan, Oakland, California
Recruitment success

• >98% of eligible families participated in the CHDS between 1959 and 1967.
• CHDS collected information on over 20,000 pregnancies, from 15,000 women
Child Health and Development Studies (CHDS): population-based multi-generational cohort

- **F0**: 1959-1967
  - F0 Enrollment at Pregnancy, Age ~ 26
    - (N=15,528)

- **F1**: 1959-1967
  - F1 Births, Age 0
    - (N=20,754)
  - 2010-2013 Adult Female F1 Follow-up
    - Age ~ 50 (N~3,000)

- **F2**: 2010-2013
  - Female F2 Enrollment
    - Ages 8-38 (N=736)
Interviews provide prospective risk factors

- Socio-economic (F0, F1, F2)
- Demographics (F0, F1, F2)
- Behavior (F0, F1, F2)
- Pregnancy history (F0, F1, F2)
- Attitudes and stressors (F0, F1)
Medical records for accurate health data

- Medical conditions 6 months before and during pregnancy, and labor and delivery (F0)
- Prenatal weight and blood pressure, hemoglobin, albumin and urinary glucose (F0)
- Growth and development (F1)
- Cancer (F0, F1)
Blood samples enable assays for biomarkers and environmental exposures

- Over 65,000 serum samples \((F0+F1+F2)\)
- Drawn at each trimester, post-partum \((F0)\)
Examination studies provide further life-course perspective on F1 and F2

- Exams at ages 5, 9-11, 15-17, 30, 44, 50 \( (F1) \)
- Exam at age 20 \( (F2) \)
- Biospecimens at age 30, 50 \( (F1) \)
- Biospecimens at age 20 \( (F2) \)
Residence, Cancer and Deaths Tracked

- Residence history
- Link to the California Cancer Registry
- Link to the California and National Death files
Birth Year and Ages of CHDS Generations

Year of Birth

Age

0 10 20 30 40 50 60 70 80 90

F0
F1
F2
F3
Exposure & Outcome Windows Count:
DDT and Mother’s (F0) Breast Cancer
MOTHERS (F0): pregnancy \( p,p' \)-DDT associated with breast cancer before age 50 for women exposed before puberty

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)

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

https://doi.org/10.1093/jnci/djy198
DDT and Daughter’s (F1) Breast Cancer
**F1:** *in utero* o,p'-DDT increases risk of breast cancer

Cohn, La Merrill, Krigbaum, Yeh, Park, Zimmermann, Cirillo; JCEM 2015 [10.1210/jc.2015-1841]
Translation: ‘Omics Linked to Epidemiologic Findings
Multiple biological systems are potential targets and mediators of exposure effects.

In utero DDT is associated with differentially methylated regions (DMRs) for three breast cancer-related genes, CCDC85A, CYP1A1, and ZFPM2, shown here.

Metabolome Wide Association Study of serum DDT and DDE in Pregnancy and Early Postpartum


https://doi.org/10.1016/j.reprotox.2019.05.059
Gly, Ser, Ala & Thr
- Betaine
- Phosphoserine
- Threonine
- Serine

Arg, Pro, Asp & Asn
- Urea cycle
- Citrulline
- Arginine
- Creatinine
- Proline

Glycerophospholipid
- PS (40:6)
- GroPIns
- Linoleate
- Linolenate
- Arachidonate

FA biosynthesis/metabolism
- Carnitine shuttle
- Linolenylcarnitine
- Palmitoylcarnitine
- Diheptanoylcarnitine
- Cervonylcarnitine

Sialic acid
- Galactose
- Hexose phospho.
- Glucono-1,5-lactone
- Glucose

Amino acid response
- DDT
- DDE

Fatty acid response
- DDT
- DDE
Transdisciplinary Team Science: Developmental Toxicology
The metabolic association of \( p,p' \)-DDT recapitulated in mouse model

- Urea cycle/amino group
- Ala & Asp metabolism
- Gly, Ser, Ala & Thr
- Tyr metabolism
- Arg & Pro metabolism
- Vitamin B3 metabolism
- Lys metabolism

Hu X Et al., Reprod Toxicol. 2019. Epub 2019/03/02. doi: 10.1016/j.reprotox.2019.05.059
Transdisciplinary Team Science: Bioinformatics for Biomarker Discovery
Understanding mixed environmental exposures using metabolomics via a hierarchical community network model in CHDS in the 1960’s

Shuzhao Li Et al, doi.org/10.1016/j.reprotox.2019.06.013
A small number of metabolic phenotypes may account for the response to a large class of environmental chemicals.

Shuzhao Li Et al, doi.org/10.1016/j.reprotox.2019.06.013
The significant communities (p<0.05) associated with F1 breast cancer. Red higher in cases; blue lower in cases.

Shuzhao Li Et al, doi.org/10.1016/j.reprotox.2019.06.013
A number of legacy chemicals like DDT have been linked to many adverse health outcomes.

Many were banned in the 1970s and the significant reduction in serum levels we find by comparing the mothers to their daughters in CHDS affirms that policy changes can lead to protection.

Despite these reductions, African Americans in the CHDS had excess serum levels for more of the 24 measured environmental chemicals in both mothers and the daughter’s generation.

This continued disparity suggests that African Americans have sustained a disproportionate body burden that may contribute to poorer health outcomes in African Americans.
Summary

• DDTs predict breast cancer in mothers depending on age at exposure and age at outcome
• *In utero* DDTs predict breast cancer in daughters and correlate to epigenetic changes in their breast cancer-related genes
• Environmental chemicals may share common metabolism pathways leading to prevention opportunities
• Disparities in environmental exposures occurred in the 1960s and continue in the next generation.
• Environmental exposures may play a role in health disparities.
Special Issue *Reproductive Toxicology*
“Womb to Breast Cancer”

Barbara A. Cohn and Mary Beth Terry
Guest Editors

DUE by March 2020
OPEN ACCESS
What about Grandchildren?

• Now completing work on DDT during grandmother pregnancy and risk in their granddaughters. Stay tuned!
Future of CHDS

• CHDS is the only opportunity for 3 and 4 generation cancer research on environmental chemicals.
• Seeking funds to secure the cohort for the future of science: to store biospecimens, communicate with CHDS members and enroll great-grandchildren.
• Please contact me if you have ideas or can help.
We Thank Funders

California Breast Cancer Research Program several critical awards most notably our Three Generations of Breast Cancer Study (15ZB-0186)

National Institutes of Health (Multiple Institutes over 60 years but mainly NICHD)

State of California which created and supports the California Cancer Registry, The Vital Status and Department of Motor Vehicle Files – without which this cancer birth cohort could not exist.
It takes a village... really more like a state and nation
Metabolome Wide Association Study of serum DDT and DDE in Pregnancy and Early Postpartum


https://doi.org/10.1016/j.reprotox.2019.05.059