Hidden Science: The Complexity of Determining what Causes Breast Cancer

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Outline

• Windows of susceptibility (WOS)
• The Case of DDT
• Resources for WOS research
• The promise of trans-generational research
Human Studies: WOS for the Breast

- In the womb
- Puberty
- Pregnancy
- Postpartum?
- Peri-menopause?
In the Womb

Higher Risk
- Longer birth length
- Higher birth weight
- Older mother
- Older father
- Diethylstilbestrol (DES) exposure?

In the Womb

Lower Risk

- Maternal pre-eclampsia or eclampsia
- Twin membership

Puberty

Higher Risk

- Early menarche.
- Tallness at an early age, particularly in combination with tallness in adulthood.
Pregnancy

Lower Risk

- Pregnancy
  - Early age at first pregnancy and last pregnancy
  - High parity
- Lactation
- Pre-eclampsia/reduced placental function
Post-partum or Peri-menopause

- ???????????????????????
Atomic Bomb Survivors

- Radiation: the only established environmental risk factor for breast cancer.
- Excess risk limited to survivors who were mostly under the age of 20 at time of exposure.
Summary-WOS Evidence

Human and animal studies:

- Environmental factors interact with stages of breast development.
- Studies that do not consider WOS are probably limited.
When Replication Fails:
DDT and Breast Cancer as a Case Study
The great expectations held for DDT have been realized. During 1946, exhaustive scientific tests have shown that, when properly used, DDT kills a host of destructive insect pests, and is a benefactor of all humanity.

Pennsalt produces DDT and its products are among those that are bringing health and safety through the insecticidal powers of Pennsalt DDT products. ... and DDT is only one of the country's largest producers of this amazing insecticide.
GOOD FOR FRUITS — Bigger apples, juicier fruits that are free from unsightly worms . . . all benefits resulting from DDT dusts and sprays.
Knox FOR THE HOME—helps to make healthier, more comfortable homes... protects your family from dangerous insect pests. Use Knox-Out DDT Powders and Sprays as directed... then watch the bugs "bite the dust"!
Knox Out for Dairies—Up to 20% more milk . . . more butter . . . more cheese . . . tests prove greater milk production when dairy cows are protected from the annoyance of many insects with DDT insecticides like Knox-Out Stock and Barn Spray.
GOOD FOR STEERS—Beef grows meatier nowadays... for it's a scientific fact that—compared to untreated cattle—beef-steers gain up to 50 pounds extra when protected from horn flies and many other pests with DDT insecticides.
PROTECT YOUR CHILDREN
Against Disease-Carrying Insects!

Trimz DDT
CHILDREN'S ROOM WALLPAPER
and Ceiling Paper

KILLS FLIES, MOSQUITOS, ANTS
... as well as mites, bedbugs, silverfish and other household pests after contact!

ADVERTISMENT DISCOURAGES many motorists insured in 50's, few in 60's and carry harmonic. However also recognizes the dangers that are present when disease-carrying insects invade the home. Actual tests have proved that one fly can carry as many as 1,500 bacteria. Imagine the hazards breed especially to children from fly-infested quarters!

Non-hazardous to children or adults, to pets or children. Certified to be absolutely safe for homes too. Darred and recommended by Parent's Magazine.

CONSUME EFFECTIVE AGAINST DISEASE-CARRYING INSECTS FOR 1 YEAR. Actual tests have proven that insect-killing properties still effective after 7 years of use.

NO SPORTS OR SITES FOR PESTS. No connection, as rule, between the DDT in paint or other paper, it can't run all.

BUDDIES! "Duck and DDT" or "Diney Peeate" — same new paints that prove in their hundreds of millions.


TRIMZ READY-PIASTED WALLPAPER

Another Product of TRIM CO., INC., DIVISION OF TRIM COMPANY

World's Leading Designer and Largest Manufacturer, Metropolitan Art, Chicago 9, Illinois

Women's Home Companion 117

Come to where the flavor is. Come to Marlboro Country.
Composition of Commercial DDT

\[ p,p'\text{-DDT} \rightarrow p,p'\text{-DDE} \]

\[ o,p'\text{-DDT} \]
Rate of Elimination*

\[ o,p'\text{-DDT} \gggg p,p'\text{-DDT} \gg p,p'\text{-DDE} \]

Detection of DDT in Human Serum*

1972 DDT Banned

1976 - 1980

DDE was convenient but...

- DDE is unlikely to accurately reflect exposure to \( p,p' \)-DDT decades earlier.
- Not surprisingly DDE measured in adults is *not* a risk factor for breast cancer in more than 19 studies.
- But, adult studies do not test exposure to DDT-related compounds during WOS
The Child Health and Development Studies (CHDS)

Resource for WOS Research
In the beginning...

• In the 1950’s the National Institutes of Health became interested in funding studies of pregnancy and child health and development.

• A novel understanding was emerging that illness and exposures during pregnancy (such as German measles and Thalidomide exposure) could have an impact on both the health of the mother, the health of the fetus, and the subsequent development of the child.
How the CHDS began…

• The CHDS recruited all pregnant women who were using Oakland Kaiser services.

• The CHDS lab provided all routine blood work for free as incentive to participate in the study. At the same time the CHDS collected blood to store for future study.

• Women completed a thorough interview about their health, previous pregnancies, this pregnancy, their health behavior and their husband’s health behaviors. These interviews took up to 4 hours and were completed over the course of a woman’s pregnancy.
Recruitment success

• Over 15,000 women participated in the CHDS between 1959 and 1967.

• Many women had multiple children in the study and so the CHDS collected information on over 20,000 pregnancies.

• > 90% participation rate
Mother’s Interview data

From interview: socio-economic, demographic, and behavioral variables for both mothers and fathers, and pregnancy history and pregnancy-related information.
Mother’s Medical Record data

From medical records:
• prenatal measures (weight and blood pressure, hemoglobin, albumin and urinary glucose)
• mother’s medical conditions 6 months before and during pregnancy, and labor and delivery
Over 65,000 serum samples are stored (frozen) at the National Cancer Institute in the Frederick Central Repository. Samples were drawn in most pregnancies at each trimester of pregnancy and at post-partum. These samples enable assays for markers of immune function, hormone levels and environmental exposures.
Children’s Data from Pediatric Visits

All children were followed through age 5:

- Repeated heights and weights (growth)
- Congenital Anomalies
- Medical conditions
Childhood Follow-up Studies

Baseline
N=20,000 pregnancies

1st Five-Year Old Study
N=5,000

2nd Five-Year Old Study
N=3,500

9-11-Year Old Study
N=4,000

Adolescent Study
N=2,000
Add Cancer and Mortality

The CHDS routinely links its files with:

- California DMV to determine residence
- California Vital Statistics to determine causes of mortality
- California Cancer Registry to determine cancer diagnoses
CHDS: A National Treasure that continues…

• The archive of data already collected is truly a treasure with potential for more study and even greater scientific yield.

• Studies of adult CHDS daughters and sons add information about how prenatal, infant and childhood exposures and behavior affect long-term health.
DDT Exposure and Breast Cancer Before Age 50

Barbara A. Cohn, Mary S. Wolff, Piera M. Cirillo, Robert I. Sholtz

Design-Maternal Breast Cancer Study

- Breast cancer cases diagnosed <50 years of age
- 129 case-control pairs
- Archived serum collected 1959 - 1967
- Before DDT was banned
- During pregnancy WOS
- Mean 17 years before diagnosis
- Mean age at blood draw 26 years
Findings discordant with prior studies

- Substantial association of \( p,p' \)-DDT 
  during pregnancy with breast cancer.
- Significantly stronger effect for women who could have been exposed before puberty.
Interaction with Age at Exposure

- Sample divided in quartiles by age in 1945 when DDT was widely introduced in U.S.
- Proxy for exposure by stage of breast development (WOS)
- Example: women over age 14 in 1945 not exposed during early breast development.
$p,p'$-DDT Associations with Breast Cancer

![Graph showing odds ratios for different age groups and tertiles.](image)
Why Departure from Prior Studies?

As a Result

- $p,p'$-DDT above limit of detection in all subjects
- Nearly 6-fold higher than in most prior studies based on blood drawn later.
- Prior studies probably misclassified earlier, more relevant exposure.
Median $p,p'$-DDT in 13 Studies

- California 1963
- L.I., NY 1996

Values in micrograms/gram lipid.
DDT Compounds by Year of Blood Draw:

13 Breast Cancer Studies with $p,p'$-DDT reported

- $p,p'$-DDE
- $p,p'$-DDT

Micrograms per gram of lipid

Year:
- 1960
- 1970
- 1980
- 1990
- 2000
Why Departure from Prior Studies

4. Measured exposure during pregnancy, a critical period of breast development.

5. Measured exposure at a young age (26 years).

6. Assessed interaction between pregnancy exposure and timing of earlier exposure.
Consistent with Animal Studies

“Exposure to carcinogens in-utero or pre-conceptually plays an important role in determining susceptibility to postnatal exposure to carcinogens”

Yamasaki, Loktionov, Tomatis, 1992, EHP vol. 98, pp.39-43
Consistent with Radiation Studies

- Findings are consistent with what is known about breast cancer in atomic bomb survivors where effects were observed only for women exposed under age 20.
Weaknesses

• Year of birth is a proxy for exposure *in utero* and during puberty.
• Exposure during pregnancy was the only exposure measured.
• Other unknown exposures may co-vary with DDT levels observed and with year of birth.
• Cannot rule out host factors including rate of metabolism.
Conclusions

• Interaction of $p,p'$-DDT with critical periods of breast development is supported by this one study.
  – In-utero
  – Puberty

• Exposure to $p,p'$-DDT during pregnancy may be associated with breast cancer.
Conclusions

• Replication of studies with the same design flaw is not informative, despite consistency.
Conclusions

• Paucity of human studies with long follow-up are a barrier to research on environmental causes of breast cancer.
• Lack of discovered modifiable risk factors in humans.
• Despite decades of investigation based on adult exposures.
Power of Multi-generation Studies

• Exposure during early development can be measured.
• Common pathways for different outcomes may exist.
• Generation-specific effects can be identified.
2\textsuperscript{nd} Generation CHDS Findings

- Prenatal DDT and DDE exposure predict time to pregnancy in daughters.
  
  \textit{The Lancet, 361:2205-06, 2003}

- Prenatal PCB exposure predicts time to pregnancy in daughters

  \textit{Reproductive Toxicol Apr 2011;31(3):290-6}

- Prenatal DDT and DDE exposure predict testicular cancer in sons.

  \textit{Arch of Occup & Env Health 2010;65(3):127-34.}
The New Frontier: Transgenerational Effects

• Non-genomic alterations in gene expression that can be transmitted across generations.
• Three generations at minimum required for investigation.
• Requires > 50 years of observation in humans
Ongoing Environmental Breast Cancer Research in the CHDS

PEDIGREE
Breast Cancer Project: 3 Gs

AIMS

• First womb to breast cancer study: effects of environmental chemicals
• Initiate active follow-up of >4,000 daughter-granddaughter sets.
• Study disparities in exposures.
3 Gs Collaborators

- Myrto Petreas, and June-Soo Park, California Department of Toxic Substances Control, California EPA
- Nina T. Holland, University of California, Berkeley.
- The California Breast Cancer Research Program
- Marj Plumb, Plumbline Consulting
- The 3 Gs Executive Advisory Committee:
  Janice Barlow, Leslie Bernstein
  Mina J. Bissell, Julia G. Brody,
  Crystal D. Crawford, Laurie Havas, Claudine Torfs,
  Ida Washington, Deborah Wingard, Irene Yen,
  Marion Kavanaugh-Lynch, Catherine Thomsen
PEDIGREE
Prenatal and Pregnancy Environmental Determinants of Intergenerational Risks

CHDS study funded by Breast Cancer and the Environment Research Program (BCERP)
Breast Cancer and the Environment Research Program (BCEREP)

- Collaboration between researchers, breast cancer advocates and community partners to explore how the environment interacts with genes to cause breast cancer.

- Joint program of NIEHS and NCI.
PEDIGREE Partners

• Marj Plumb, DrPH, MNA, Plumpline Coaching and Consulting, Inc. works with CHDS to design, construct, train and facilitate the Participant Advisory Panel
• Mary Beth Terry, PhD, Columbia University, expert on mammographic density, Multiple PI with Barbara Cohn
• The Participant Advisory Council (PAC)
What is PEDIGREE?

Exciting opportunity for the CHDS to:

- Establish a Participant Advisory Council (PAC)
- Collect additional data that builds on the adult studies and expands research opportunities
How does PEDIGREE expand research opportunities?

• Collect additional mammograms to examine whether daughters of mothers with breast cancer are more susceptible to prenatal exposures.
• Examine bio-specimens collected from adult daughters for changes in the DNA structure.
• Determine feasibility of attaining pathology reports/tissue for daughters with breast cancer.
• Expand prior maternal study on DDT and breast cancer.
Imperatives

• Enroll the daughters’ cohort before more cases are diagnosed.
• Enroll granddaughters promptly to observe their reproductive period.
• Engage cohort members to minimize loss to follow-up.
• Find funds for parallel study in males to study prostate cancer and other outcomes.
Imperative!

- Find funding source for continuing long-term follow-up.
Summary

• Human studies are consistent with the hypothesis that both exogenous and environmental risk factors for breast cancer interact with stages of mammary gland development early in life:
  
  • *In utero*
  
  • During puberty
  
  • During pregnancy
Summary

- Study designs based on adult exposures are not adequate tests of effects.
- Replication of null findings in studies of adult exposure is not sufficient to rule out human effects.
Summary

• Existing long-term cohorts can be address windows of susceptibility.
• Builds on prior investment.
• Decades of follow-up are completed.
• Can study outcomes related to breast cancer including reproductive health, body mass, behavior.
Summary

• Investment in long-term follow-up is critical to determine the impact on environmental exposures on the breast.
• And other outcomes of great interest to the public health.
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- NICHD
- NCI
- NIEHS
- CA Breast Cancer Research Program
Additional Resources

• Public Health Institute
  ➔ www.phi.org

• Child Health and Development Studies
  ➔ www.chdstudies.org

• Three Generations Study/Environmental Causes of Breast Cancer across Generations
  ➔ www.chdstudies.org/3gs

• Disparities Study/A Lifecourse Approach to Emerging Health Disparities in a U.S. Cohort
  ➔ www.chdstudies.org/research/index.php#study2

• Breast Cancer and the Environment Research Program
  ➔ www.bcerc.org