Environmental Pollution and Breast Cancer: Adding Epidemiological Studies to Biological Evidence

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Committee on Breast Cancer and the Environment

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Outline

• Method and scope of review
• Methodological challenges
• Examples of results from more precise research questions
• Communications issues
• Future priorities
Sources

- Review of literature through 2006
  - Published in Cancer, 2007
  - Detailed in online databases
  - [silentspring.org/sciencereview](http://silentspring.org/sciencereview)

- Epidemiology update in progress 2010
Environmental pollutant terms

- Environmental pollutants
- Drinking water, water quality
- Air pollution, traffic, auto exhaust
- Organochlorine, pesticides, solvents
- PCBs, dioxin, PAHs, specific OCs, etc.
- Occupation
- Chemicals ID’d as mammary carcinogens
Critical review questions

How good is the ... 

- exposure measure?
- comparison?
- causal model?
The FDA does not safety test personal care products before they go to market. Some endocrine disruptors are used to create cosmetics, such as ethynyl estradiol and 1,2-propylene glycol.

**Review Articles**

- Environmental Pollutants and Breast Cancer (pdf)
- Diet and Breast Cancer (pdf)

**EVIDENCE FROM HUMANS**

In a systematic search of scientific research indexed in the online medical resource PubMed, we identified 450 primary epidemiologic research articles on breast cancer and environmental pollutants, physical activity, body size, and prospective studies of dietary factors.

For each article, the Science Review database includes quick access to basic study information and critical assessments:

- the bibliographic citation and abstract or a link to a copyrighted abstract
- information about the study population, exposure assessment method, study design, results, and analyses of ethnic minority populations, early life exposures, or interactions with inherited genes
- assessments of the study's strengths and weaknesses, and
- interpretation of the study's results

Articles are searchable by topic. In addition, the database includes about 50 citations to review articles, methods papers, and exposure assessments that aid in interpreting the primary research. The database includes studies of environmental pollutants published through June 2006 and in other topic areas through May 2005. Review methods are described in the review articles published in Cancer, as listed to the left.
Chemicals of Interest

- Mammary carcinogens damage DNA
- Endocrine disruptors as tumor promoters
  - Tamoxifen, HRT
- Endocrine disruptors as developmental toxicants that alter susceptibility
  - DES
Example Mammary Carcinogen Exposures

- ionizing radiation
- gasoline
- auto exhaust, air pollution
- paint remover, solvents
- flame retardants
- pesticides
- moldy grain
- water disinfection byproducts
- nonstick coatings

- benzene
- PAHs
- ethylene oxide
- methylene chloride

*Rudel et al., 2007, Cancer*
Example Endocrine Disruptor Exposures

- pesticides
- food packaging
- laundry detergent
- hair spray
- fragrances
- floor finishes
- sunscreen
- plastics
- disinfectants
- furniture
- soybeans
- lavender
Limited # and scope of human breast cancer studies of environmental pollutants

• 2007 Review: 152 articles
  – 7 report on early life exposures
  – 28 analyzed risk among nonwhites
  – Late-life organochlorines in blood are most-studied

• Update:
  55 new articles to July 2010
Topics remain limited 2006-2010

<table>
<thead>
<tr>
<th># of New Articles</th>
<th>Primary Topic Area</th>
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<tr>
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<td>Pesticides</td>
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<tr>
<td>15</td>
<td>Occupation</td>
</tr>
<tr>
<td>9</td>
<td>PAH's</td>
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<tr>
<td>4</td>
<td>PCB's</td>
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<tr>
<td>3</td>
<td>Dioxin</td>
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<tr>
<td>3</td>
<td>Other</td>
</tr>
<tr>
<td>2</td>
<td>Drinking Water</td>
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<tr>
<td><strong>55</strong></td>
<td><strong>Total</strong></td>
</tr>
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</table>

Number of New Articles by Topic Area (n=55)

- **Pesticides**: 35%
- **Occupation**: 27%
- **PAH's**: 16%
- **PCB's**: 7%
- **Dioxin**: 6%
- **Other**: 5%
- **Drinking Water**: 4%
Methodological challenges

• Exposure assessment!
  – Lack of measurement techniques for most target compounds
  – Lack of contrast - Everyone’s exposed
  – Difficult to ID high-exposed women
  – Need to address biologically active mixtures and co-occurring compounds
  – Need for measurements across life cycle
  – Lack of access to target tissue
Exposure Measures: No “Gold Standard”

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<tr>
<th>Time</th>
<th>Agent</th>
<th>Pathway</th>
<th>Dose</th>
<th>Latency</th>
<th>Development</th>
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<td>Job</td>
<td></td>
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<tr>
<td>GIS</td>
<td>location, records, models</td>
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<tr>
<td>Environmental</td>
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<tr>
<td>Biomarker</td>
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</table>
More methodological challenges

• Effect size may be small
• Effects may be via other bc risk factors
  – age at menarche, body size, etc.
• Individual differences in susceptibility
• Disease outcomes heterogeneous
  – Pre- vs. post-menopausal disease, hormone receptor status, etc.
What we know

• Most chemicals with plausibly relevant biological activity have never been assessed in a human breast cancer study

• Late-life blood levels of DDE are not associated with breast cancer risk in general populations

• Breast cancer causation is multi-factorial and complex, with risk factors across the lifespan
  – Hard to be confident study design asks right question
Clues for further study

• Examples of more precise research questions incorporate exposure timing, genetic susceptibility, age at diagnosis, etc.
  - DDT exposure in girlhood
  - TCDD exposure at younger age
  - PCBs: and genetic variation, race/ethnicity
  - Organic solvents: in younger workers, in combination with exhaust, in drinking water
  - PAHs: and genetic variation, assessed by historical geographic model
1945: DDT use began

1959: use peaked

1965: DDT peaked in diet

1972: banned in USA

1959-1967: Blood sampled in women giving birth

Through 1998: Breast cancer diagnosed

Cohn 2007

This study: DDT in early life, yrs before disease

Other studies: DDE (anti-androgen, multiple sources including current diet) in late adulthood, at diagnosis
p,p’-DDT: Cohn, 2007

- 129 cases diagnosed < age 50
- Higher risk for women born after 1931 (exposed < age 14)
- No association for DDE (consistent with others)
Dioxin (TCDD): Seveso, Italy

• Zones A, B, & R based on soil TCDD concentrations

Figure 1
Map of the Seveso, Italy area, including the territory of 11 towns. The map indicates the three dioxin-contaminated zones with decreasing mean soil levels (A, B, and R) and the surrounding non-contaminated zone adopted as the reference. Taken from Pesatori, 2009
Dioxin (TCDD): Seveso, Italy

  - 981 females who were infants to 40 years old in 1976 and resided in Zones A and B
  - Followed for breast cancer incidence through 1998
  - HR 2.1 (95%CI: 1.0-4.6) per 10-fold increase in serum TCDD
  - Follow-up is continuing (Eskenazi, ISEE-ISES 2010)
PCBs, CYP1A1 and Breast Cancer Risk

![Bar chart showing odds ratios](image)

- **Low Gene Activity / Low PCB**
- **High Gene Activity / High PCB**

Odds Ratio

- Moysich 99: 2.9
- Laden 02: 2.8
- Zhang 04: 4.3
- Li 05: 2.1

(Adapted from Moysich)
PCBs pooled analysis, Moysich

• Data from 7 studies
  – WNY (Moysich/Freudenheim)
  – NHS (Laden)
  – Carolina (Millikan)
  – Long Island (Gammon/Wolff)
  – NYC (Wolff)
  – Connecticut (Zhang)
  – Clue (Helzlsourer)

• >2000 breast cancer patients and > 3000 controls

• More detailed classifications of PCB exposure and CYP1A1 genotypes
Quartiles of lipid adjusted total PCBs and breast cancer risk

Moysich, preliminary

Moysich, preliminary
Quartiles of lipid adjusted total PCBs and breast cancer risk

Caucasian

African-American

Moysich, preliminary

www.silent springs.org
Associations between CYP1A1*2C genotypes and breast cancer risk by PCBs body burden

Moysich, preliminary
Organic Solvents

TCE in drinking water


(Employed > 10 y)  (Exposure relevant to Camp Lejeune)
Males in jobs exposed to gasoline and vehicle exhaust  (Hansen 2000)
PAHs: Long Island Breast Cancer Study Project

- Large population-based case control study

**Detectable PAH-DNA Adducts and Breast Cancer Risk**

Gammon, 2002

<table>
<thead>
<tr>
<th>Group</th>
<th>Odds Ratio</th>
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<tr>
<td>Overall</td>
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<tr>
<td>&lt;65 years</td>
<td>1.48</td>
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<tr>
<td>65+ years</td>
<td>1.18</td>
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<tr>
<td>Premenopausal</td>
<td>1.58</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>1.19</td>
</tr>
</tbody>
</table>
PAHs & Genetic Variability

Detectable PAH-DNA Adduct Levels and Genetic Polymorphisms

DNA Repair
Deactivation of PAH intermediates
Apoptosis
Air Pollution, Traffic

- Erie and Niagara Counties, New York
  - Population-based case-control study

Bonner, 2005: Total suspended particles (TSP)
Nie, 2007: Geographic traffic exposure model

### Premenopausal Women

- At birth: 1.78
- At Menarche: 2.07
- At First Pregnancy: 1.22

### Postmenopausal Women

- At birth: 2.42
- At Menarche: 1.45
- At First Pregnancy: 1.33
Overview: Human Studies of Pollutants

• Some evidence of links to breast cancer
  – Organochlorines: DDT, PCBs, Dioxin
  – Organic solvents
  – PAHs, air pollution

• Clear evidence of complexity

• Large knowledge gaps

• Strong biologically-based hypotheses
• What is the public health translation of these very limited results?
  – For example, for PCBs
Factors with **uncertain, controversial, or unproven effect** on breast cancer risk

A great deal of research has been reported and more is being done to understand possible environmental influences on breast cancer risk.

Of special interest are compounds in the environment that have been found in lab studies to have estrogen-like properties, which could in theory affect breast cancer risk. For example, substances found in some plastics, certain cosmetics and personal care products, pesticides (such as DDE), and PCBs (polychlorinated biphenyls) seem to have such properties.

Although this issue understandably invokes a great deal of public concern, at this time research does not show a clear link between breast cancer risk and exposure to these substances. Unfortunately, studying such effects in humans is difficult. More research is needed to better define the possible health effects of these and similar substances.
Blood organochlorine levels (exposure to certain types of pesticides and industrial chemicals)

Environmental pollutants have been suggested as potential causes of breast cancer because many of these compounds have estrogen-like traits. Some of the most common and well-studied environmental pollutants are organochlorines. These include the pesticide DDE (1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene) and industrial chemicals, such as PCB's (polychlorinated biphenyls). One way to measure exposure to these chemicals is by looking at their levels in a person’s blood. The results of most studies looking at blood organochlorine levels and risk of breast cancer, including the Long Island Breast Cancer Study, have found no link between the two [388-393].

Sometimes a cluster (small areas, such as a town or county, where rates of breast cancer are higher than the U.S. average) is found and this raises interest in possible environmental causes of breast cancer. Examples of such clusters include Long Island, New York and Marin County, California [390,394]. To date, no environmental toxins related to breast cancer have been found. This does not mean that there are no environmental pollutants that can increase risk of breast cancer. However, most clusters have been explained by differences in risk factors such as ages at menarche and menopause and number of children.
Factors not likely related to risk.

Although not as well-studied as the factors described above, based on the research to date, the factors below are not likely related to breast cancer risk.

**Plastics**

Links between plastics and cancer are often reported by the media and in e-mail hoaxes (one e-mail hoax falsely claims to be a study from Johns Hopkins University). However, there is no scientific research to support a link between using plastic items, such as drinking water from a plastic bottle, and the risk of breast cancer.
The following have been proven not to be risk factors for breast cancer or their effects on breast cancer risk are not known:

Abortion

There does not appear to be a link between abortion and breast cancer.

Oral Contraceptives

Taking oral contraceptives ("the pill") may slightly increase the risk of breast cancer in current users. This risk decreases over time. The most commonly used oral contraceptive contains estrogen.

Progestin-only contraceptives that are injected or implanted do not appear to increase the risk of breast cancer.

Environment

Studies have not proven that being exposed to certain substances in the environment (such as chemicals, metals, dust, and pollution) increases the risk of breast cancer.

Diet

Diet is being studied as a risk factor for breast cancer. It is not proven that a diet low in fat or high in fruits and vegetables will prevent breast cancer. For more information on diet and health, see the Fruits and Veggies website.

Active and passive cigarette smoking

It has not been proven that either active cigarette smoking or passive smoking (inhaling secondhand smoke) increases the risk of developing breast cancer.

Statins
Other information resources

• Silentspring.org
• envirocancer.cornell.edu (not updating)
• erbc.vassar.edu
• breastcancerfund.org/clear-science
“Studies have not proven”

- Translation should be grounded in an understanding of what kind of evidence
  ...is attainable in a particular timeframe
  ...is a meaningful basis for prudent action
What kind of evidence?

President’s Cancer Panel 2010

“...an environmental health paradigm for long-latency diseases is needed to enable regulatory action based on compelling animal and in vitro evidence before cause and effect in humans has been proven.”

p.99
Cancer Prevention Science

Biological mechanism + Human exposure → Basis for action

Brody, 2010
Priority: Exposome

• Immediately focus resources on environmental exposure assessment
  
  – Why:
    • Establish priorities for research and action
    • Provide tools for human studies
  
  – What
    • Expand chemical targets
    • Develop large-scale, non-intrusive, less expensive methods (dust, passive air sampling)
    • Include lifespan exposures
    • Address mixtures, cumulative impact
    • Assess sources, pathways as well as biological measures
    • Identify and study high-exposed people
    • Integrate environmental measures and support major cohort studies (Sisters, CA Teachers, Ntl Childrens, BCERP, Shanghai)
A “small” influence on breast cancer risk touches many lives

- We regulate chemical cancer risks at 1 in a million for many reasons
Thanks

• 2010 updated epidemiology review
  - Stephanie H. Chan, University of Washington
• 2007 Review (in Cancer)
  - Ruthann A. Rudel, Silent Spring Institute
  - Kathleen Attfield, Silent Spring Institute/Harvard
  - Kirsten Moysich, Roswell Park Cancer Institute
  - Karin Michels, Harvard University
  - Leslie Bernstein, City of Hope
  - Olivier Humblet, Silent Spring Institute/Harvard
A Healthier Future

View a brief introduction to Silent Spring Institute’s research on the links between the environment and breast cancer, environmental health issues and the emerging field of green chemistry.

Featured Research

Tests find new contaminants in Cape Cod’s drinking water supply

President’s Cancer Panel highlights everyday exposures to environmental pollutants and cancer

Oil refinery found near homes

Pollution from household and personal care products has been a blind spot for society, according to study

Media Coverage

Household Exposure Study highlighted by the NIEHS’ Gwen Collman, The Environmental Factor

Director of Research, Ruthann Rudel, participates in review of soy infant formula, The

New at Silent Spring Institute

Massachusetts Environmental Trust funds Silent Spring Institute research by the sale of specialty license plates

Dinner honoree, Judi Hirshfield-Bartek, interviewed by The Boston Globe

DID YOU KNOW?

Silent Spring water tests reveal contamination, Cape Cod Times

Water, WCVB-TV

Supporters of Silent Spring Institute Dinner, May 6

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Today’s Environmental Health News

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