Breast Cancer & the Environment: The Growing Evidence

Presented by:

Ruthann Rudel, MS
Director of Research
Silent Spring Institute

Megan Schwarzman, MD, MPH
Research Scientist
Center for Occupational and Environmental Health, University of California, Berkeley
Agenda

- What is being done to reduce exposures to toxic chemicals
- Studying environmental links to breast cancer
- Developing improved methods for identifying toxic chemicals
- What you can do to help strengthen chemical safety in the US
Our Mission

*Breast Cancer Action carries the voices of people affected by breast cancer in order to inspire and compel the changes necessary to end the breast cancer epidemic.*
BCAction’s Strategic Priorities

(1) Putting Patients First

(2) Creating Healthy Environments

(3) Eliminating Social Inequities
Presenter slide

Ruthann Rudel, MS
Silent Spring Institute
Environmental Chemicals and Breast Cancer

Opportunities for Prevention

Ruthann Rudel
Breast Cancer Action webinar June 2014
"... the true burden of environmentally induced cancer has been grossly underestimated"
Breast cancer in a global context

- The most common cancer in women worldwide.
- Incidence is rising in developing nations.\(^1\)
- Risk changes when women migrate

1. Forouzanfar, M. Breast and cervical cancer in 187 countries between 1980 and 2010: a systemic analysis

www.silent spring.org
Breast cancer risk factors

- Family history
- Ionizing radiation
- Reproductive history – menarche, menopause, births
- Overweight after menopause
- Pharmaceutical hormones: HRT, DES
- Alcohol
- Lack of physical exercise
- Tobacco smoke

Carcinogens / Hormones
How might environmental chemicals play a role?
What kinds of studies reveal cancer causes?

- High, well-defined exposures among large groups

<table>
<thead>
<tr>
<th></th>
<th>No disease</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not exposed</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>Exposed</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
</tbody>
</table>
What kinds of studies reveal cancer causes?

• Occupational studies
  – Men, chemicals, cancers (not breast)

• Accidents/disasters (e.g. ionizing radiation)
• Pharmaceuticals (e.g. HRT)
First lawsuit for breast cancer from DES settled in 2012

60+ years to develop human evidence of DES-breast cancer link

“Every Group 1 agent can be considered to represent cancers that might have been prevented had scientists been able to predict cancer hazards earlier or had public health authorities been willing to act more quickly when scientific information became available.”

Cogliano et al. 2011 based on review of >100 IARC carcinogens in IARC Monograph vol. 100
Cancer Prevention Science

- Biological mechanism
- Human exposure

Basis for action

- Educate
- Regulate
- Reformulate

Strength of evidence, not "proof"
Biological Mechanisms

- Mammary carcinogens damage DNA
- Endocrine disruptors as tumor promoters
- Endocrine disruptors as developmental toxicants that alter susceptibility

Before

After

Incoming UV Photon

Estrogen stimulation

Mistake in DNA duplication

Increased proliferation

"Really?"

Yes... desPLEX to prevent ABORTION, MISCARRIAGE and PREMATURE LABOR
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
Rudel et al., 2014 EHP

www.silent spring.org
The breast is vulnerable during development

- Before birth
- Puberty
- Pregnancy
We need chemicals testing to prevent breast cancer

Yet only 3% of National Institutes of Health $$ goes for environmental health
What does chemical safety testing have to do with breast cancer?

We want . . .

– *chemicals evaluated for safety*

– *tests relevant to breast cancer*
Animal models and in vitro (cell-based)

- Identify potential carcinogens
- Reveal mechanisms
- Used for drug discovery and chemical safety testing
Animal studies

- 216 chemicals found to cause mammary tumors in rodents

- Animals typically exposed only as adults

Rudel et al. 2007 Cancer
Animal studies

- Rats aren’t people!
- But rodent and human results **are** generally consistent

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Human Breast Cancer</th>
<th>Rodent Mammary Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRT (E + P)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HRT (E)</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>Oral Contraceptives (E + P)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>DES</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Griseofulvin, Furosemide,</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>Metronidazole</td>
<td></td>
<td></td>
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<tr>
<td>Indomethacin, Nitrofurantin</td>
<td>(-)</td>
<td>+</td>
</tr>
<tr>
<td>Ionizing radiation</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Alcohol</td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td>Heterocyclic amines (meat)</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>Sleep disruption</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>Ethylene oxide</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>PAH</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>Solvents</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>DDE (tested in adult)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DDT (early exposure)</td>
<td>(+)</td>
<td>Not tested</td>
</tr>
<tr>
<td>PCBs (testing adults, entire</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>population)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCBs (polymorphism)</td>
<td>(+)</td>
<td>Not tested</td>
</tr>
<tr>
<td>Dioxin (early exposure)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
</tbody>
</table>

**Key**

| Pink & orange (+)                  | Positive association |
| Blue (-)                           | Negative association  |
New Exposure Biomarkers as Tools For Breast Cancer Epidemiology, Biomonitoring, and Prevention: A Systematic Approach Based on Animal Evidence

Rudel et al. 2014 Environmental Health Perspectives

17 Everyday Chemicals Could Be Linked to Breast Cancer

Scientists who looked at data linking mammary tumors in animals to vehicle exhaust, paint removers, disinfectants and other common items, and compared it to more limited data for humans, say there’s cause for concern.
Future: Faster, cheaper chemical safety tests
Because chemical exposures are so widespread, even a "small" influence on cancer risk touches many lives.
7 TIPS TO REDUCE EXPOSURE TO LIKELY BREAST CARCINOGENS

A wide variety of everyday chemicals cause mammary tumors in animals. That’s worrisome evidence the chemicals may increase breast cancer risk. While scientists continue to learn more about how these chemicals affect humans, there is enough information to reduce our exposures now.

- Lessen exposure to fumes from gasoline and to exhaust from diesel or other fuel combustion. Support anti-idling and fuel efficiency regulations.
- Use a ventilation fan when you cook, and limit consumption of burned or charred food.
- Find a dry-cleaner who doesn’t use PERC or other solvents; ask for “wet cleaning.”
- Use a solid carbon block drinking water filter. Help keep your drinking water clean by protecting source waters.
- Avoid stain-resistant rugs, furniture and fabrics. Tell retailers and manufacturers you don’t want PFCs in your home—or in the Arctic, where these persistent chemicals build up.
- Ask for furniture that doesn’t contain flame retardants, including in the foam. If flame retardant free foam isn’t available, choose furniture made from naturally flame-resistant fabrics and padding such as wool, hemp, polyester, latex, down, or leather. Choose rug pads made from felt, jute, or rubber rather than foam.
- Since chemicals accumulate in house dust, remove shoes at the door, vacuum with a HEPA filter, and clean with a damp rag or mop.

None of us can prevent breast cancer alone. Organizations like Safer Chemicals, Healthy Families can help you take national action. Learn more at www.saferchemicals.org.
THE BREAST CANCER AND CHEMICALS POLICY PROJECT

Megan Schwarzman, MD, MPH
UC Berkeley School of Public Health
Core question

What body of information –obtained using existing test methods– could best identify chemicals that may increase the risk of breast cancer?
Project Goals

1. **Design an approach** for identifying chemicals that may contribute to the development or progression of breast cancer;

2. **Identify research needs** and recommend improvements to existing test methods; and

3. **Pilot a model process** that can be applied to other disease endpoints, as a step toward the ultimate aim of producing a comprehensive approach for identifying hazardous chemicals.
Expert panel

- Susan Braun, MA - Commonweal
- Vincent James Cogliano, PhD - WHO International Agency for Research on Cancer
- Shanaz Dairkee *, PhD - California Pacific Medical Center Research Institute
- Suzanne Fenton, PhD - National Institute of Environmental Health Sciences
- William H. Goodson III, MD - California Pacific Medical Center Research Institute
- Joe Guth *, PhD, JD - Science and Environmental Health Network
- Dale Johnson, PharmD, PhD - University California Berkeley & Emiliem
- Jean Latimer, PhD - School of Medicine University of Pittsburgh
- Ron Melnick, PhD - National Institute of Environmental Health Sciences
- Rachel Morello-Frosch, PhD, MPH - University of California Berkeley
- Ruthann A. Rudel, MS - Silent Spring Institute
- Gina Solomon*, MD, MPH - UCSF & Natural Resources Defense Council
- Carlos Sonnenschein, MD - Tufts University School of Medicine
- Lauren Zeise*, PhD Cal/EPA Office of Environmental Health Hazard Assessment

* Indicates a member of the core panel, which met monthly throughout the project
Steps of the Breast Cancer and Chemicals Policy Project

**STEP 1**
Identify toxicity "endpoints", alterations in biological processes that increase the risk of breast cancer

**STEP 2**
Identify toxicity testing methods to detect chemicals that alter biological processes relevant to breast cancer

**STEP 3**
Propose an approach for prioritizing and testing chemicals for their ability to raise the risk of breast cancer: the HIA-BC

**STEP 4**
Pilot test the proposed HIA-BC by investigating how well-studied chemicals would perform if tested

**STEP 5**
Compare assays in the HIA-BC with those in Federal chemical testing initiatives
Step 1. Events Associated with Breast Cancer

<table>
<thead>
<tr>
<th>Cellular &amp; Molecular Events</th>
<th>Tissue Changes</th>
<th>Susceptibility Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alterations in hormone levels, metabolism or receptors</td>
<td>Genotoxicity</td>
<td>Obesity</td>
</tr>
<tr>
<td>Changes in gene transcription &amp; translation</td>
<td>Oxidative stress</td>
<td>Early onset of breast development</td>
</tr>
<tr>
<td>Cell cycle changes</td>
<td>Immune modulation</td>
<td>Alterations in cyclicity</td>
</tr>
<tr>
<td>Peptide hormones (growth hormones)</td>
<td>Limitless replication potential</td>
<td>Genetic polymorphisms in metabolizing enzymes</td>
</tr>
<tr>
<td></td>
<td>Evasion of apoptosis</td>
<td>Duration of lifetime estrogen exposure</td>
</tr>
<tr>
<td></td>
<td>Self-sufficiency in growth</td>
<td></td>
</tr>
</tbody>
</table>
Step 2: Identify test methods (schematic)

<table>
<thead>
<tr>
<th>Model System</th>
<th>Detectable Events Affecting Breast Cancer Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Molecular Mechanisms</td>
</tr>
<tr>
<td></td>
<td>Gene Expression</td>
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<tr>
<td>In Silico</td>
<td></td>
</tr>
<tr>
<td>In Vitro</td>
<td></td>
</tr>
<tr>
<td>In Vivo</td>
<td></td>
</tr>
<tr>
<td>Epidemiological</td>
<td></td>
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</tbody>
</table>

http://coeh.berkeley.edu/greenchemistry/cbcrpdocs/matrix.pdf
Step 3. Hazard Identification Approach for Breast Carcinogens (HIA-BC)

Consists of three parts:

- Prioritization step
- Rapid Screening Methods
- In vivo studies
Step 3. HIA-BC: Chemical Prioritization

**Chemical Prioritization**
Chemicals, their metabolites and degradation products, should be prioritized for testing based on the following parameters:

<table>
<thead>
<tr>
<th>Hazard indicators</th>
<th>Exposure potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>including structural similarities to other mammary gland carcinogens, or indicators that a chemical or its possible metabolite have endocrine activity, alter breast development or gene expression, or create genetic mutations.</td>
<td>predicted by physical-chemical properties that indicate potential for bioaccumulation, persistence in the environment, or result in exposure to breast tissue. Also those identified by biomonitoring, environmental monitoring, or other proxy measures such as high production volume or dispersive use in consumer products or workplaces. Exposure potential should be assessed across the entire human life-cycle, and the product lifecycle from manufacturing through disposal.</td>
</tr>
</tbody>
</table>
### Step 3. HIA-BC: Rapid Screening Methods

#### Hazard Identification Approach

**Rapid (in vitro) screening**

**Genotoxicity**
- Mutagenicity (e.g., Ames or equivalent)
- Chromosome aberrations (e.g., OECD TG 473)
- Micronuclei formation (e.g., OECD TG 487)
- DNA strand breaks (e.g., COMET assay)

**Cell cycle changes**
- Cell division (e.g., $^3$H thymidine proliferation assay)
- Altered apoptosis (e.g., TUNNEL assay)

**Endocrine disruption**
- Activation or inhibition of:
  - Estrogen-mediated transcription (e.g., E-screen)
  - Androgen-mediated transcription (e.g., A-screen)
- Enzymes specific to synthesis or metabolism of estrogen, androgen or progesterone (e.g., aromatase activity assay)
Step 3. HIA-BC: *In Vivo* Studies

Hazard Identification Approach

**Animal studies (in vivo): development and maturation**

- Genotoxicity in breast epithelial cells
  - Mutagenicity
  - Chromosome aberrations
  - Micronuclei formation
  - DNA strand breaks

- Precursor changes, biomarkers and induction of mammary gland tumors
  - Modification of existing long-term cancer bioassays* redesigned to evaluate mammary gland endpoints, and:
    - include whole mounts of mammary tissue
    - include in utero exposures
    - assess effects over the whole lifespan
    - use an animal strain appropriate to the exposure and the endpoint

- Cell cycle changes in breast epithelial cells
  - Cell proliferation
  - Decreased apoptosis

- Endocrine disruption
  - Estrogenic activity (e.g., Uterotrophic assay)
  - Androgenic activity (e.g., Hershberger assay)
  - Developmental changes in female and male mammary gland tissue (e.g., TEB formation, ductal branching, ER and AR levels)
  - Reproductive changes in males and females (e.g., AGD, nipple retention, altered cyclicity, pubertal timing)
  - Altered circulating hormone levels (e.g., steroid or peptide hormones)
Notes on the Hazard Identification approach for Breast Carcinogens (HIA-BC)

Panel recommended endpoints to test, not specific assays

- The field of toxicity testing is rapidly evolving
- Best practices can evolve with emerging tests

High throughput screens are under development

- Potential to test thousands of chemicals at a range of doses
- Potential to address metabolic differences by testing many possible metabolites
### Step 4: Pilot Testing the HIA-BC

<table>
<thead>
<tr>
<th>Known to cause breast cancer in women</th>
<th>Some evidence of breast cancer in women</th>
<th>Animal mammary carcinogens</th>
<th>Chemicals with suggestive evidence</th>
<th>Carcinogens with no evidence of breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>DDT</td>
<td>Acrylamide</td>
<td>Atrazine</td>
<td>Arsenic</td>
</tr>
<tr>
<td>Diethylstilbestrol</td>
<td>TCDD (dioxin)</td>
<td>Benzene</td>
<td>Androstenedione</td>
<td>Asbestos</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Ethylene oxide</td>
<td>1,3-Butadiene</td>
<td>Dihydrotestosterone</td>
<td>Lead (inorganic)</td>
</tr>
<tr>
<td>Conjugated estrogens (CE)</td>
<td>Tobacco smoke</td>
<td>Dimethylbenzanthracene</td>
<td></td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>HRT (CE + MPA)</td>
<td>Medroxyprogesterone acetate (MPA)</td>
<td></td>
<td></td>
<td>Chemicals not known to cause cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFOA</td>
<td>Caprolactam</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vinyl chloride</td>
<td>Benzalkonium chloride</td>
</tr>
</tbody>
</table>
Step 5: Comparing the HIA-BC Assays To Assays Used In Federal Chemical Screening Initiatives

ToxCast – Environmental Protection Agency

Tox21- Interagency (NIEHS, NTP, EPA)

Endocrine Disruptor Screening Program (EDSP)
Recommendations

Chemical toxicity testing—and the public policies that require it—can inform breast cancer prevention efforts by identifying chemicals that may raise the risk of breast cancer.

1. Chemical testing relevant to breast cancer should include the following endpoints:
   - Genotoxicity
   - Cell cycle changes
   - Endocrine disruption (e.g., estrogenicity)
   - Altered mammary gland development

2. Design and conduct toxicity tests to consider:
   - Timing of exposure
   - Underlying susceptibility factors (e.g., genetic variability, concurrent exposures)

3. Further research should:
   - Increase understanding of the biological pathways associated with breast cancer
   - Adapt current testing methods to improve their relevance for breast cancer
   - Develop and validate new toxicity tests, including high throughput screening methods

4. Apply a similar process to other disease endpoints to develop a comprehensive approach to identifying chemicals of concern.
More Information

Full BCCP report available online
http://coeh.berkeley.edu/greenchemistry/cbcrp.htm

Advocacy materials:
- Booklet (spanish translation)
- Fact sheet (spanish, chinese, korean)
- Freely available online at
  http://coeh.berkeley.edu/greenchemistry/cbcrp.htm

Journal articles:
- Overview article on BCCP project and findings (in revision at Environmental Health Perspectives)
- Commentary on need to study mammary gland developmental endpoints (special issue of Reproductive Toxicology October, 2014)
State of Chemical of Reform

- 3 bills introduced in the last 2 years
  - The Safe Chemicals Act of 2013
  - Chemical Safety Improvement Act (CSIA)
  - Chemicals in Commerce Act (CICA)
- Growing interest in updating Toxic Substances Control Act 1976 (TSCA)
- Tell your Senators to support strong chemical regulation
- Encourage your local representatives to support state chemical reform policies
Review emails/website mentioned in the presentation

- Science reviews detailed in online databases: silentspring.org/sciencereview
- Chemicals & Breast Cancer Advocacy materials http://coeh.berkeley.edu/greenchemistry/cbcrp.htm
Join BCAction!

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Toll-free: 877-2STOPBC
Breast Cancer Action

Challenging Assumptions. Inspiring Change.

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www.thinkbeforeyoupink.org