Using Toxicology to Advance Breast Cancer Prevention

Ruthann Rudel

SOT/RASS Webinar

September 10, 2014
Outline

• What do we know about breast cancer, and how did we learn it?
• Three biological pathways to chemically-induced breast cancer
• Chemicals that cause rodent mammary gland tumors
• New exposure biomarkers for surveillance and epidemiology
Breast cancer

• Leading cause of death in women from their mid 30s - early 50s
• Most common invasive malignancy in women
• Treatment costs ~ $17B/year (US)
• Costs of death and disability from breast cancer ~$88B (Globally; ACS)
Reducing relevant exposure will reduce risk

Breast cancer incidence dropped when older women went off HRT.
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

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Similarities between established risk factors and potential breast carcinogens

- reproductive factors
- Rx hormones
- alcohol
- ionizing radiation
- (tobacco smoke)

environmental EDCs

- solvents
- genotoxicants (esp DSB-inducing)
- PAHs

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The breast is vulnerable during development

• Before birth
• Puberty
• Pregnancy
How might chemicals increase breast cancer risk?

- Damaging DNA
- Ionizing radiation
- Promoting tumor growth
- Disrupting development -> vulnerability

DES
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><strong>Not exposed</strong></td>
<td><img src="image1" alt="Diagram" /></td>
<td><img src="image2" alt="Diagram" /></td>
</tr>
<tr>
<td><strong>Exposed</strong></td>
<td><img src="image3" alt="Diagram" /></td>
<td><img src="image4" alt="Diagram" /></td>
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</tbody>
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What kinds of studies reveal cancer causes?

- Occupational studies
  - Men, chemicals, cancers (not breast)

- Accidents/disasters (e.g. ionizing radiation)

- Pharmaceuticals (e.g. HRT)
Diethylstilbestrol (DES)

Prescribed to pregnant women in 1940s-60s

60+ years to develop human evidence of breast cancer link

Hoover et al, 2011

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Prevention

“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

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Biological plausibility

• International Agency for Research on Cancer (IARC), which has declared that “it is biologically plausible that agents for which there is sufficient evidence of carcinogenicity in experimental animals also present a carcinogenic hazard to humans.”
Animal and human studies

- 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, Metronidazole</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>Indomethacin, Nitrofurantoin</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>
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<tr>
<td>PAH</td>
<td>(+)</td>
<td>+</td>
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<tr>
<td>Solvents</td>
<td>(+)</td>
<td>+</td>
</tr>
<tr>
<td>DDE (adult exposure)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DDT (early life exposure)</td>
<td>(+)</td>
<td>Not tested</td>
</tr>
<tr>
<td>PCBs (general population)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PCBs (polymorphism)</td>
<td>(+)</td>
<td>Not tested</td>
</tr>
<tr>
<td>Dioxin (early life exposure)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
</tbody>
</table>

+ Stronger evidence of association

(+) Limited evidence of association

(-) Limited evidence for no association

Stronger evidence for no association

Rudel et al 2014 Environmental Health Perspectives
Animal Mammary Gland Carcinogens

• 216 chemicals
  – 29 High Production Vol. (>1 million lbs/yr)
  – 35 air pollutants
  – 73 in consumer products
  – 25 had > 5,000 women workers exposed
  – 10 were food additives
  – 47 pharmaceuticals

Rudel et al., 2007 Cancer
Limitations and considerations

- Rodent bioassay is likely insensitive to some mechanisms
  - Early life exposure, altered susceptibility, weak promotors
- These MCs vary in strength of evidence, potency
- Site concordance is not expected, but is common and informative
Likely human relevance indicated by mutagenicity, multi-species tumors

- 93 of 132 IARC chemicals - “sufficient” evidence in animals
- 84% with some evidence of mutagenicity
- CPDB analysis – multi-species carcinogens
  - 91% rat MC also caused tumors in mice (any site)
  - 89% mouse MC also caused tumors in rat (any site)
- 34 of 39 NTP MCs also caused tumors in other species; only 6 both MC
methylen chloride
CAS RN 75-09-2

Chemical Summary

Exposure and Risk Assessment

Cancer Studies

Originating list
Carcinogenicity Potency Database, National Toxicology Program studies, IARC Monographs,
Chemical Carcinogenesis Research Information System

Associated chemicals
none

Major use
Chlorinated solvent

Widespread exposure
More Likely

Human exposure summary
Widespread exposure occurs during the production and industrial use of methylene chloride and during
the use of a variety of consumer products containing it. Consumer products that may contain the chemical
include: fabric cleaners, furniture polish, paint strippers, wood sealant and stains, spray paints,
adhesives, shoe polish and art supplies (SRD). Used until 1980 as a propellant for hair spray. Substantial
losses to the environment lead to ubiquitous low-level exposures from ambient air and groundwater (IARC
1999 vol.71 p.25, NTP 11th ROC).

Image from the National Library of Medicine

Cancer studies: Experimental details

National Toxicology Program Technical Report 306, 1986

Link

Notes
"Clear evidence" in rats is based on the mammary tumors. Rats: 0, 1000, 2000, 4000 ppm: benign mammary
tumors in female rats: 5/50, 11/50, 13/50, 22/50. In male rats, they looked at the combined benign mammary
tumors and the intergumentary ones, for significant increase. In Discussion, for mammary tumors they note
Burek 1980 and 1984 for mammary tumors, Nitschke 1982. For "negative" they note National Coffee
Association studies of 1982 and 1983 in which much lower levels were used (highest was 250 mg/kg).

Route
inhalation

Species
Rat, mouse

Sexes
M,F

Strain
F344/N rats, B6C3F mice

Doses
Rats: 0, 1000, 2000, 4000 ppm. Mice: 0, 2000, 4000 ppm, for 6 hrs/day, 5 days/wk for 102 weeks. 50 animals in
each group. Age exposure started 8-9 weeks for rats, 7-8 weeks for mice.

Time after cessation of dosing
1 week
102 MCs with likely exposure

- Any biomarker: 73
- Measured in humans: 62
- Measured in nonoccupational population: 45
- Measured in NHANES: 23

Some of the remaining 29 could be measured with modified versions of existing methods for related chemicals.
Priority exposures: chemical groups

• Aromatic amines
  – including TDI
• Halogenated OP flame retardants and degradation products
• Halogenated organic solvents
• Heterocyclic amines
• Hormones and endocrine disruptors
• Nitro-PAHs
• PAHs
• Pharmaceuticals
Priority exposures: individual chemicals

• 1,3-Butadiene
• Acrylamide
• Benzene
• Ethylene oxide; propylene oxide
• MX (water disinfection byproduct)
• Ochratoxin A
• PFOA, related compounds
• Styrene
Analytical methods

• Blood: parent and metabolite
• Blood: DNA adduct
• Blood: protein adduct
  – hemoglobin
  – albumin
• Urine: metabolites
• Breast milk
• Hair
• Other media
Opportunities

• Epidemiology - 42 cohort studies with 3.5 million women
  – Stored samples - are biomarkers still present?
  – Relevant exposure period? (consider latency, induction times)

• Biomonitoring - who is exposed, how can we prevent exposures

Study designs carefully matched to underlying biology will yield meaningful results
Increased investment and toxicologically-based study designs may yield payoff for epi

Breast cancer epidemiology: # articles 2006-2012

<table>
<thead>
<tr>
<th>Category</th>
<th>Articles</th>
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</thead>
<tbody>
<tr>
<td>OC pesticide</td>
<td>13</td>
</tr>
<tr>
<td>Dioxin</td>
<td>5</td>
</tr>
<tr>
<td>Occupation</td>
<td>10</td>
</tr>
<tr>
<td>Drinking water</td>
<td>5</td>
</tr>
<tr>
<td>PAH</td>
<td>10</td>
</tr>
<tr>
<td>Organic solvent</td>
<td>5</td>
</tr>
<tr>
<td>Personal products</td>
<td>7</td>
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<td>Pesticide, not OC</td>
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<td>Air pollution</td>
<td>6</td>
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<tr>
<td>Other</td>
<td>10</td>
</tr>
<tr>
<td>PCBs</td>
<td>6</td>
</tr>
</tbody>
</table>
Opportunities

• Consumer education and product formulation
  – avoid likely/plausible carcinogens?
• Regulation and testing
  – Capture more BC-relevant pathways

_Fenton et al. 2002 Tox Sci; Brown et al. 1998, Carcinogenesis_
Three major reports highlight chemicals testing as an important vehicle for cancer prevention.
What does chemical safety testing have to do with breast cancer?

Goals

– chemicals evaluated for safety
– tests relevant to breast cancer
High throughput testing for breast carcinogens

Collaboration with Chris Vulpe (UC Berkeley), ToxCast, Tox21

- MG dev disruptors 16
- Rodent MCs 67
- “non-carcinogens” 19

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21st Century Risk Assessment Challenge

• 20th century question: How much of chemical X can we put into product Y and consider it safe?
• What’s your 21st century question?
  – How can we formulate using least toxic materials with goal of sustainability throughout lifecycle?
  – How do we estimate risks across the population, considering cumulative exposures and susceptible populations?
  – How can we restructure risk assessment to reflect these questions?
Because chemical exposures are so widespread, even a “small” influence on cancer risk touches many lives.
Collaborators and funders

Silent Spring Institute
- Julia G. Brody
- Janet Ackerman
- Kathleen Attfield
- Robin Dodson
- Kathryn Rodgers
- Laura Perovich

Funders
- Avon Foundation for Women
- Susan G. Komen for the Cure

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Key Reviews

- Epidemiology and toxicology reviews
  - Brody et al., *Cancer*, 2007
  - Rudel et al., *Cancer*, 2007
  - Detailed in online databases silentspring.org/sciencereview

- Mammary gland development
  Rudel et al., *Environmental Health Perspectives*, 2011

- Measuring potential breast carcinogens in people
  Rudel et al., *Environmental Health Perspectives*, 2014