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# **The BCERP Legacy: Windows of Susceptibility to Environmental Risks of Disease**

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## Knowns and Unknowns: What We Knew Then (1997)

ANNALS *of* THE NEW YORK  
ACADEMY OF SCIENCES

Avoidable Causes of Breast Cancer: The Known, Unknown, and  
the Suspected

Davis et al., Ann NY Acad Sci, 1997

“For more than two centuries, scientists have acknowledged the  
**critical role of hormones** in breast cancer.”

“Recent [studies] reveal that **certain environmental chemicals**, including some  
plastics, pesticides, fuels, and drugs, can **disrupt hormone production** and  
**metabolism**...we speculate that **exposure to endocrine-disrupting materials**  
in the general environment accounts for some portion of breast cancer today.”

## State of the Evidence: What We Know Now (2017)

REVIEW

Open Access

State of the evidence 2017: an update on the connection between breast cancer and the environment



Gray et al., Environ Health, 2017

“Increasing **evidence from epidemiological studies**, as well as a better understanding of **mechanisms linking toxicants** with development of breast cancer, all reinforce the conclusion that **exposures to these substances** – many of which are found in common, everyday products and byproducts – **may lead to increased risk of developing breast cancer.**”

## A New Framework for Prevention Research (2019)

REVIEW

Open Access

Environmental exposures during windows of susceptibility for breast cancer: a framework for prevention research

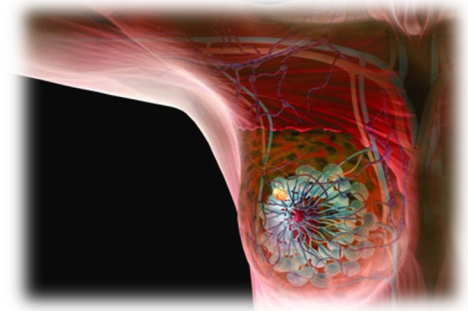


Terry et al., Breast Cancer Research, 2019

“The influence of environmental chemicals on **breast cancer risk** **may be greater** during several **windows of susceptibility** (WOS) in a woman’s life, including prenatal development, puberty, pregnancy, and the menopausal transition.”

## BCERP: A Legacy of Contributions

- BCERP researchers, advocates, and educators have made numerous contributions to help us:
  - Understand **biological mechanisms** involved in breast cancer
  - Understand how **genetic, environmental, nutritional**, and **social factors** affect risk
  - Understand how **windows of susceptibility** impact risk
  - Determine effective ways to **engage and educate** girls and women
  - Develop **meaningful partnerships** to advance **breast cancer prevention**



# BCERP History and Milestones



**1994 – 1999**

**1996:** Timing and breast cancer risk RFA

- **1993:** NCI and NIEHS initiate Northeast and Mid-Atlantic Breast Cancer Study
- **1994:** NCI and NIEHS initiate Long Island Breast Cancer Study
- **1994:** NIEHS team discovers BRCA1



**2000 – 2006**

**2003:** BCERC RFA (Phase I, 2003-2009)

- **2000:** Developmental origins of health and disease (DOHaD)
- **2001:** Workshop with NIEHS, NCI, NBCC and advocacy groups
- **2003:** The Sister Study
- **2003:** BCERC established by NIEHS and NCI



**2007 – 2012**

**2010:** BCERP RFA (Phase II, 2010-2014)

- **2007:** Foundation for NIH facilitates first collaborative summit on breast cancer research
- **2008:** NIEHS and NCI form Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC)
- **2011:** Komen-sponsored IOM report, "Breast Cancer/Environment: A Life Course Approach"



**2013 – 2019**

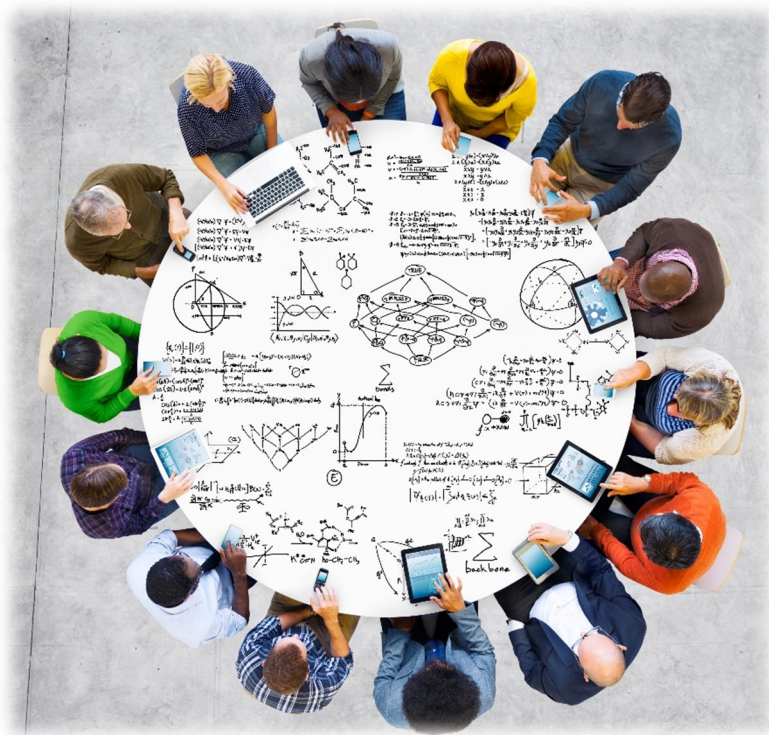
**2015:** BCERP RFA (Phase III, 2015-2020)

- **2016:** Comm. Research Initiative (2016-2018)
- **2013:** IBCERCC report, "Breast Cancer and Environment: Prioritizing Prevention"
- **2013:** BCERP Communication Toolkit
- **2017:** BCERP produce State of the Evidence Report



## BCERC and the Team Science Approach

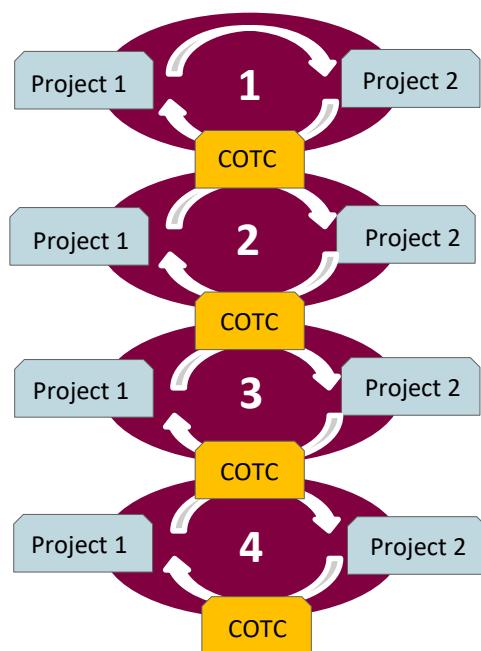
- One of the first NIEHS programs to **require transdisciplinary expertise** within one grant and under overall consortium
- Use **team science** – toxicology, epidemiology, environmental health, biostatistics, communication – to address research questions and facilitate community engagement
- Team science is now a **fundamental approach** in other NIEHS programs, including the EHS Core Centers, Partnerships for Environmental Public Health, and Research to Action



# Changes in Program Infrastructure Over Time

## Phase I (BCERC)

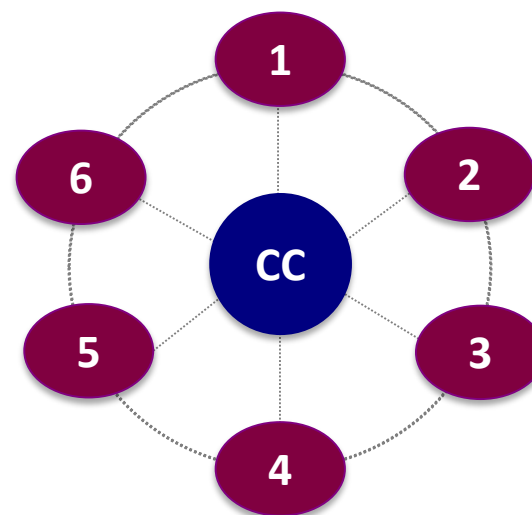
(2003-2009)



- Centers with transdisciplinary approach
- Parallel, cross-Center research projects
- Community outreach and translation cores (COTC)

## Phases II and III (BCERP)

(2010-2014; 2015-2020)



- \*Transdisciplinary research projects
  - Multi-Center/PIs
  - Basic science
  - Human/epi study
  - Community engagement
- Coordinating Center (CC)
  - Intellectual leadership
  - Cross-BCERP collaborations



## **Phase I: BCERC and Puberty Study (2003-2009)**

- Epidemiologic study involving diverse cohort of young girls to understand determinants of pubertal timing (breast development and menarche)
- Animal studies to characterize molecular features of the mammary gland and impacts of environmental exposures across life span



## **Phases II and III: BCERP Transdisciplinary WOS Studies (2010-2020)**

- Continue project aims and efforts from BCERC
- Greater emphasis on environmental influences during windows of susceptibility and impacts on breast cancer risk



## **Breast Cancer/Environment Communication Research Initiative (2016-2018)**

- Focus on translation of research findings about breast cancer and the environment that result in effective risk messaging for target audiences
- Provide scientific evidence for developing communication-based prevention efforts to reduce the risk for breast cancer from environmental factors

# Overview of BCERP Outputs

**\$ 106.3 million** Total for  
FY2003 – 2019

\$67.4 million (NIEHS)

\$38.8 million (NCI)

**26** grants



**363** publications

**RCR** (top 2, primary)

12.5 and 11.9

**294** articles

**62** reviews

**7** commentaries

**Journals** (top 3)

- *Breast Can Res.* (16)
- *Environ Health Perspect.* (13)
- *Endocrinology* (11)



## Scientific Resources Generated

- Data harmonization
- Biorepositories
- Rodent model
- Alternatives to mammogram
- Statistical model



## BCERP Expanded Toolkit

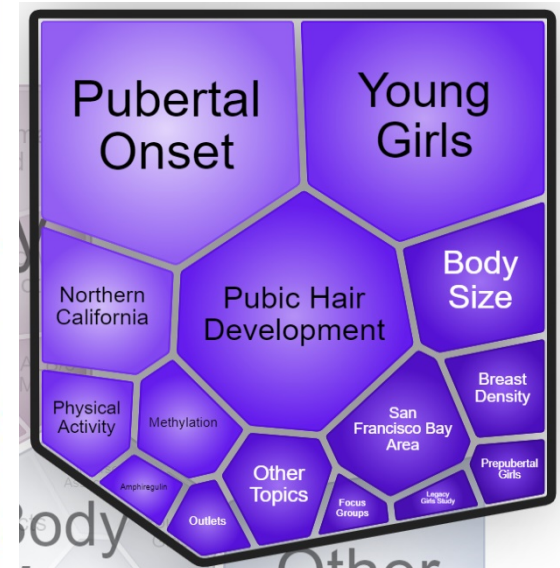
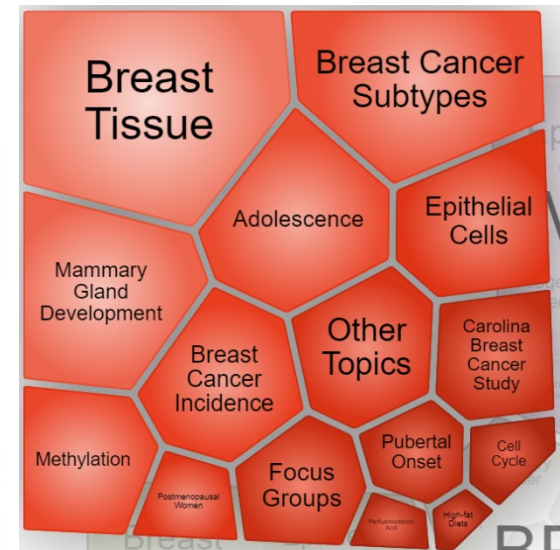
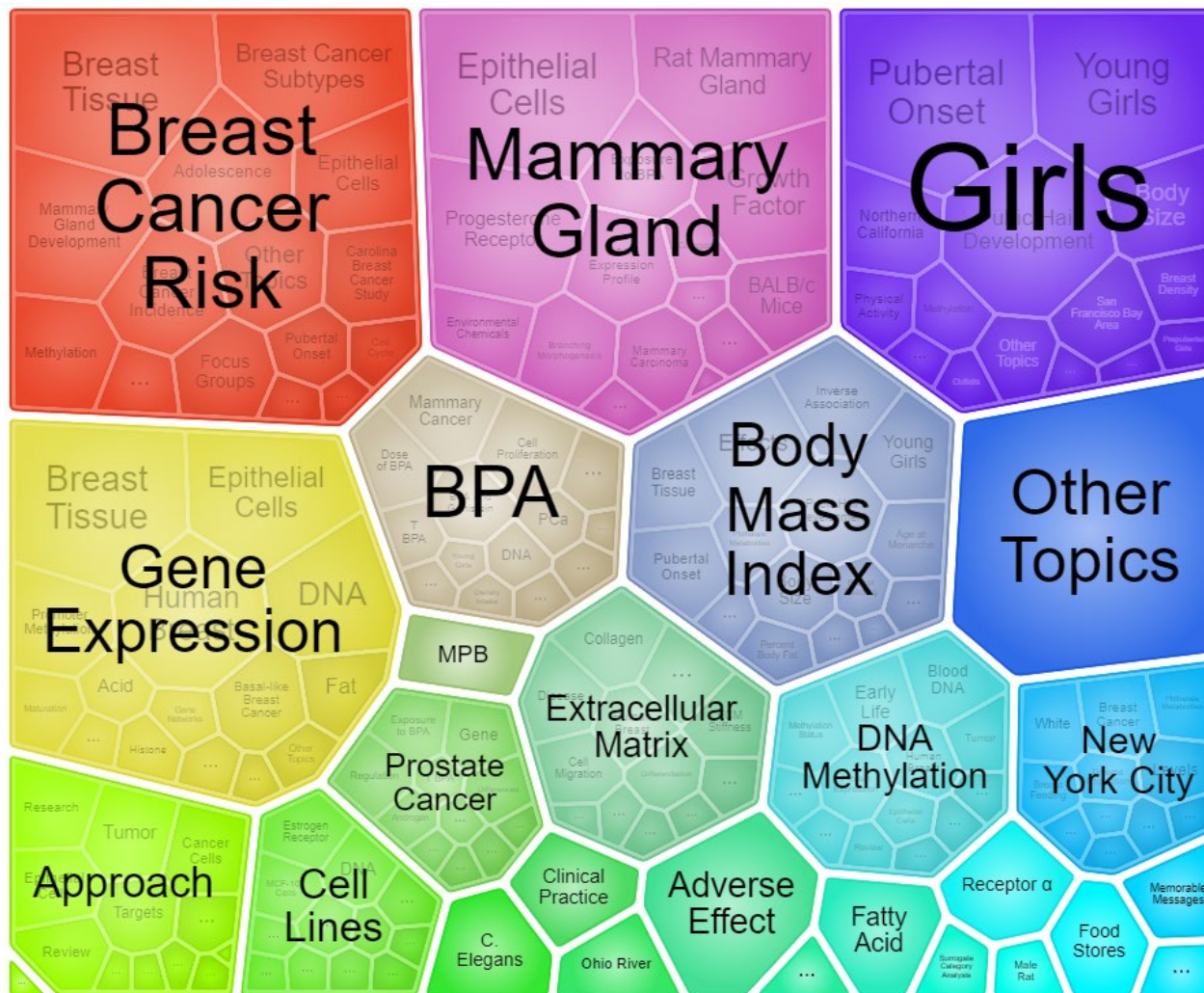
- Factsheets and brochures
- Newsletters and webpages
- Wallet-size cards
- Videos



- Glossaries
- Coloring and comic books
- Monographs
- Teaching and training modules
- Staging charts

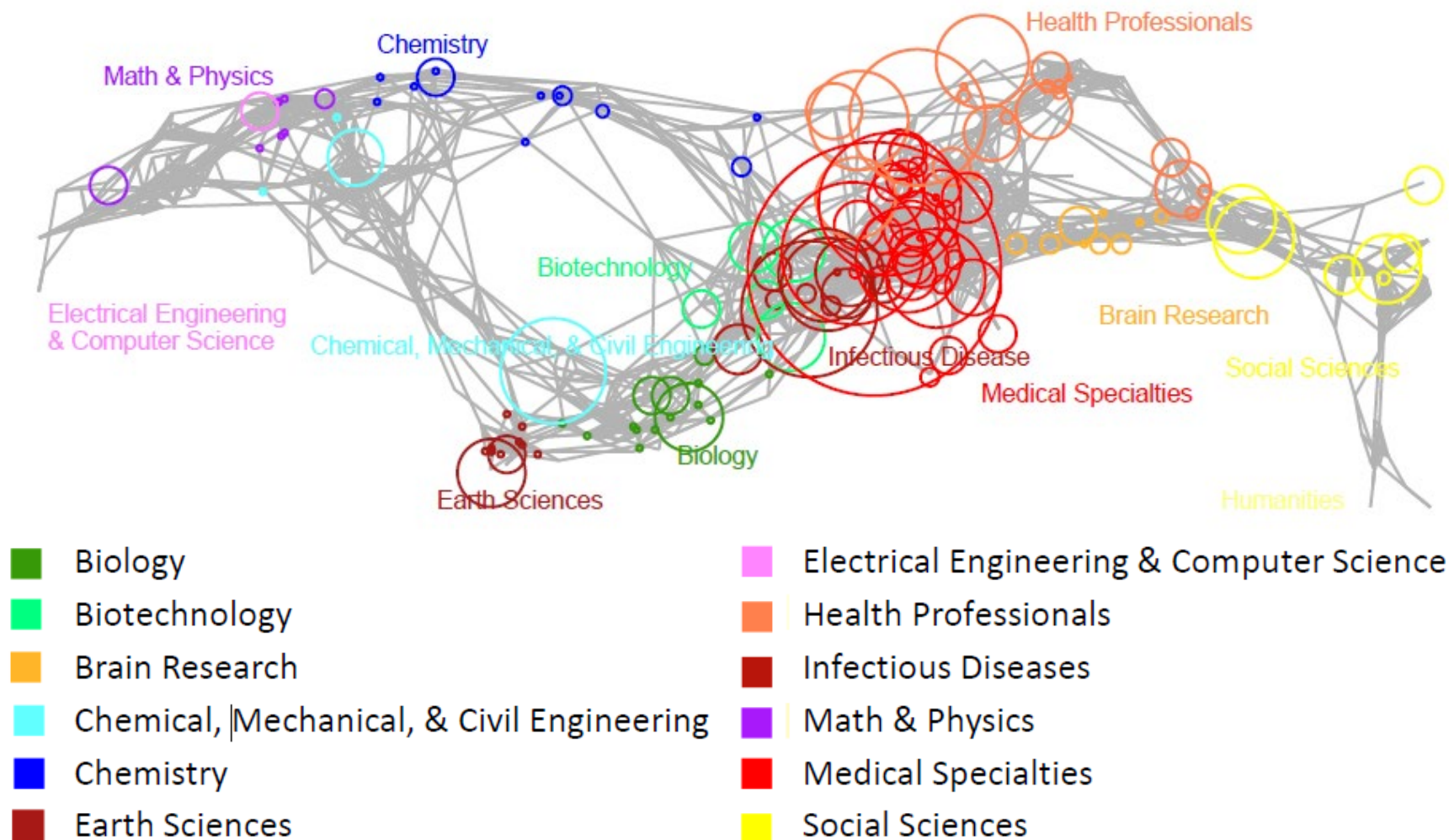


## BCERP Publication Topics





# BCERP Publication Disciplines



## Windows of Susceptibility:



**Prenatal**



**Prepuberty**



**Puberty**



**Adolescence**



**Pregnancy/  
Postpartum**



**Menopause**

## BCERP Findings: Prenatal Period as WOS

- Prenatal BPA exposure **increased breast cancer susceptibility** in rats and **shifted the WOS** for chemically-induced mammary cancer from PND50 to PND100 (Betancourt et al., Environ Health Perspect, 2010)
- Prenatal DDT exposure was associated with **alteration in genes** relevant to breast cancer in daughters (Wu et al., Reprod Toxicol, 2019)
  - Found differentially-methylated regions associated with markers of DDT in three genes important to breast cancer (CCDC85A, CYP1A1, ZFPM2)





## BCERP Findings: Prepuberty and Puberty as WOS

- Exposure to high concentrations of phytoestrogens, phthalates, and phenols **affected pubertal development** in girls (Wolff et al., Environ Health Perspect, 2010)
- African American girls from neighborhoods with more recreational outlets had lower rates of pubertal onset by age 10-12 (Deardorff et al., BMC Pediatr, 2012)
  - Physical activity may play a key role in determining **accelerated pubertal onset** among young African-American girls
- Distribution of **pubertal timing has shifted** to a younger age (Biro et al., Pediatrics, 2013)
- Duration of being breast fed was associated with **higher PFCs in girls** (Pinney et al., Environ Pollut, 2014)



## BCERP Findings: Prepuberty and Puberty as WOS

- Exposure to high concentrations of POPs correlated with **delayed pubertal onset** (Windham et al., Environ Health Perspect, 2015)
- Diets high in fat associated with an **increased risk of breast cancer** in mice (Aupperlee et al., Breast Cancer Res, 2015)
- Levels of amphiregulin, a mediator of estrogen and progesterone signaling in breast tissue, may be a predictor of **increased breast cancer risk** in pubertal girls (Biro et al., J Pediatr Adolesc Gynecol, 2017)
- **Faster epigenetic aging** associated with **faster pubertal development** in girls, which can lead to an increased risk of cancer and mortality in adulthood (Binder et al., Epigenetics, 2018)



## BCERP Findings: Adolescence and Adulthood as WOS

- High levels of serum DDT was associated with a **five-fold increased risk of breast cancer** in women who were heavily exposed to DDT during childhood and adolescence (Cohn et al., Environ Health Perspect, 2007)
  - Women not exposed to DDT before age 14 showed no association between later DDT exposure and breast cancer
- Low, but not high, BPA doses **accelerated mammary tumorigenesis** and metastasis in a genetically distinct mouse model (Jenkins et al., Environ Health Perspect, 2011)
  - Women with erbB2 positive breast cancer may be particularly susceptible to chronic BPA exposure in adulthood



## BCERP Findings: Pregnancy and Postpartum as WOS

- Postpartum exposure to PCBs was strongly associated with increased risk of early breast cancer (Cohn et al., Breast Cancer Res Treat, 2012)
  - High levels of the three PCB congeners resulted in a **three-fold increase in breast cancer risk**
  - Risk for early breast cancer likely depends on congener mixtures and individual response to multiple exposures
- Mice exposed to oxybenzone during pregnancy and lactation experienced alterations to their mammary gland function and morphology (LaPlante et al., J Endocr Soc, 2018)
  - Oxybenzone is an endocrine-disrupting chemical found in sunscreen and personal care products
  - The mice were treated with **doses relevant to human exposures**





## BCERP Findings: Menopause as WOS

- Combination of estrogen and progesterone **stimulated tumor proliferation** in postmenopausal rats compared with tumors growing in the presence of estrogen alone (Kariagina et al., Horm Cancer, 2013)
- Premenopausal hysterectomy may **reduce the long-term risk** of breast cancer (Robinson et al., Am J Epidemiol, 2016)
- Postmenopausal women receiving estrogen + progestin hormone replacement therapy face **increased risk for breast cancer** (Aupperlee et al., Transl Oncol, 2018)
  - Estrogen + progestin hormone replacement therapy regulates the cell cycle inhibitor p27 which would normally mediate progestin-induced proliferation of breast tumors
- PBDE exposure causes endocrine disrupting activity in breast cancer cells (Kanaya et al., Toxicol Sci, 2019)



## BCERP Findings Inform Dissemination and Implementation

- Breast cancer news coverage **rarely includes modifiable factors**, like lifestyle and chemical exposures  
(Atkin et al., J Health Commun, 2008)
- Scientific literacy predicts knowledge gain and **lower literacy messaging** produces **higher knowledge gain**  
(Smith et al., J Health Commun, 2013)
- More knowledge led to **lower perceived risk**  
(Smith et al., Health Commun, 2017)





## Digital Exposure Report-Back Interface (DERBI)

- Reporting back research results ensures participants have access to their data and what they mean for health
- **Digital Exposure Report-Back Interface (DERBI):** Web-based tool for creating personalized chemical exposure reports and graphs for study participants (Brody / Silent Spring Institute)

### Personalized reports include:

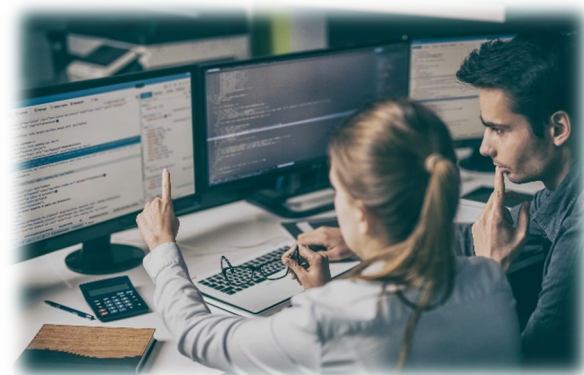
- Individual results
- Comparisons to study group and benchmark populations
- Study-wide findings
- Potential sources of exposure
- What is known and unknown about health effects
- Strategies to reduce exposure

PCB28



## BCERP Scientific Resources Generated

- Puberty studies data harmonization – more than 34,420 variables harmonized into 5,114 variables with complete documentation
- Rodent model with breast lesions that progress like human mammary tumors
- Optical spectroscopy as an alternative to mammogram for measuring breast density
- Statistical models such as accelerated time-to-failure (hazards ratios) to be used in longitudinal models

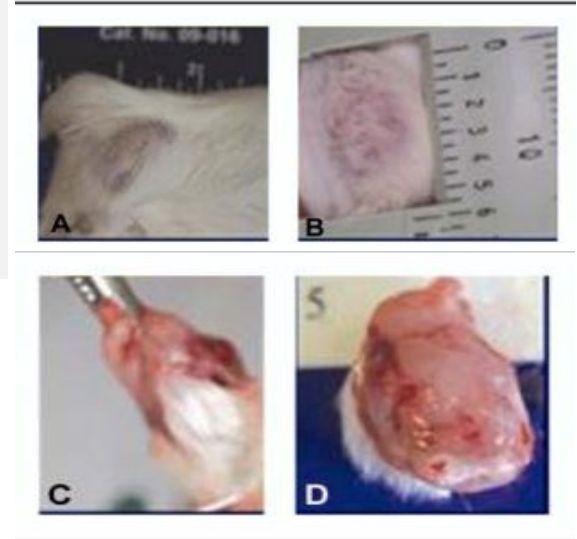


## BCERP Scientific Resources Generated

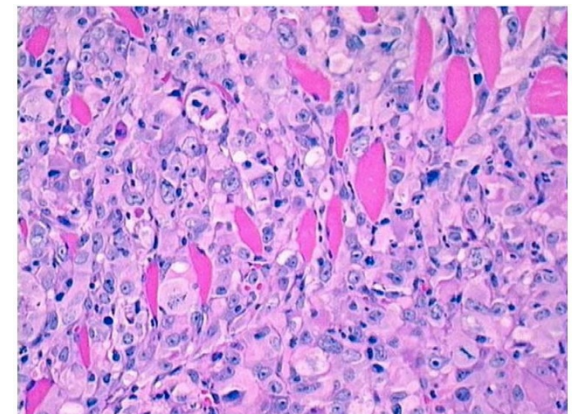
### Model of Estrogen-Induced Breast Cancer

- Developed in vitro-vivo model to explore mechanisms by which estrogens induce breast cancer
- 17- $\beta$ -estradiol (E2) induced transformation and tumorigenesis in human breast epithelial cells (HBEC)
- Injection of E2-transformed HBEC in mice led to formation of tumors in mammary fat pad

Palpable tumor formed in mouse by E2-transformed HBEC



Histological section of invasive adenocarcinoma growing in fat pad of mouse



## Translation and Education

**COTCs, community partners,** and **advocates** have played a significant role in outreach, education, and dissemination of messages

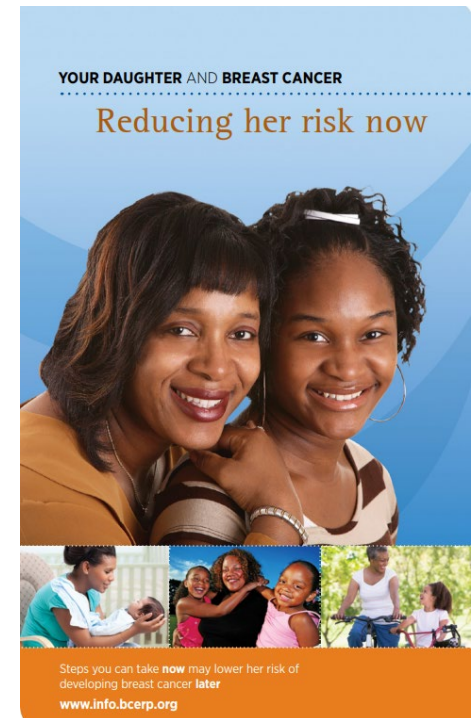




# BCERP Expanded Toolkit





Materials for **parents and caregivers, health care professionals, educators, and advocates**

- Culturally-relevant brochures and PSAs
- Fact sheets on plastics, phthalates, and other chemicals
- Newsletters and webpages
- Wallet-size cards on product risks
- Educational videos
- Comic books about breast biology and density
- Coloring books of study activities for young girls
- Medical and scientific glossaries for advocates
- Monograph for pediatricians
- Teaching and training modules for advocates
- Staging charts (breast and pubic hair) to evaluate adolescent maturation






Check the symbol on the bottom of plastic items before you buy.

**The safer plastic choices for food and beverages:**

 PETE	 HDPE	 LDPE	 PP
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**Plastics to try to avoid:**

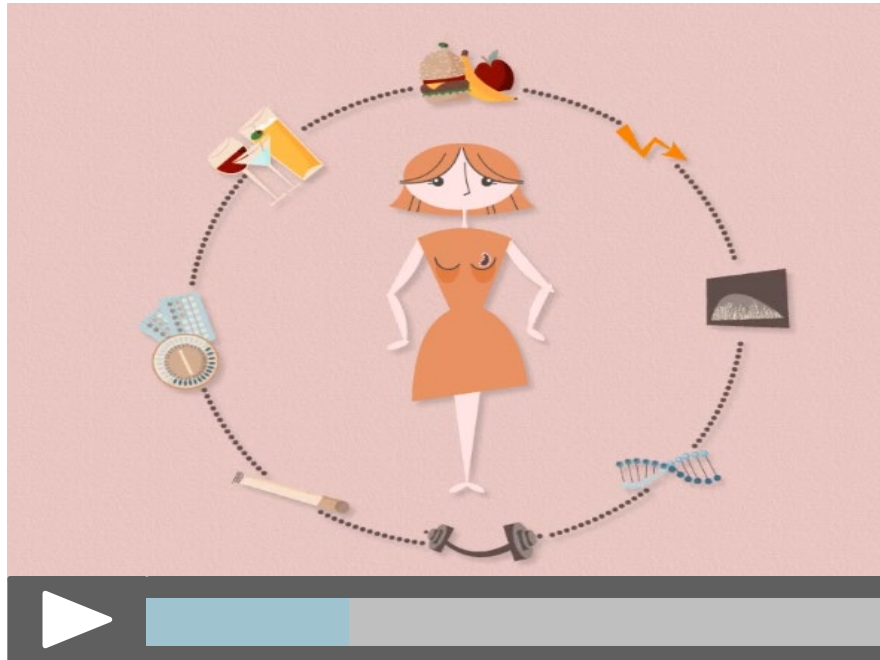
 V (Usually PVC or vinyl)	 PS (Usually Styrofoam)	 OTHER
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**Other tips for the safe use of plastics:**

1. Try not to use plastic containers in the microwave. If you can, it's safer to use glass or ceramic containers.
2. Beware of using plastic wraps in the microwave. A safer choice is waxed paper.
3. Try to reduce your use of products made of PVC, vinyl or Styrofoam.

# BCERP Expanded Toolkit

## Toolkit on Breast Density



- Breast density is a risk factor, but messaging to women is unclear
- **“What Does My Number Mean?”**  
A Basic Research Primer on Mammographic Density
- Toolkit includes **video**, **comic book** (English and Spanish), **glossary**, and **evaluation form**

### GETTING TO KNOW YOUR BREASTS

We live in a neighborhood that exists within a larger community that contributes to our well-being. The well-being of the neighborhood is maintained through:

- facilitating communication among residents by providing telephones to talk to each other,
- streets that allow people to visit each other,
- needed services, such as garbage disposal,

These services create a well-organized, functioning community that allows residents to live healthy, happy and productive lives.



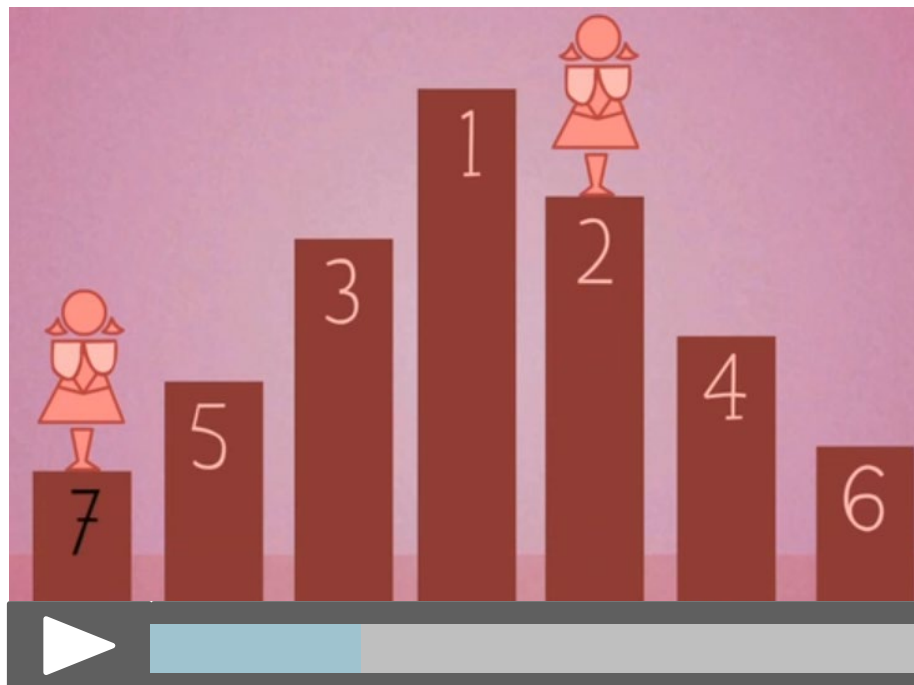
Likewise, your breast is a miniature ‘community’ whose health depends on its infrastructure that promotes communication and protection for all of the cells of the breast to maintain its long-term health and to do its job.





# BCERP Expanded Toolkit

## Video and Comic Book



- **“The Breast Biologues,”** award-winning video and **biology dialogue** about breast cancer and the environment
- Comic book available in English, Spanish, and Vietnamese



## Advocates Mentoring Advocates in NYC

- **“Advocates Mentoring Advocates”** program and toolkit created to build knowledge about environmental exposures and breast cancer risk in underserved communities
- **Model workshop and training program** prepared African American breast cancer advocates in NYC to develop a targeted and standardized education program on breast cancer and the environment
- Trainees delivered program to women in Harlem, the Bronx, and Brooklyn



Witness Project of Harlem team members who were trained and community and academic partners



# The ELLA Project and Outreach Database



- **Early Life Exposures in Latina Adolescents (ELLA) Project**
- Investigating the influence of environmental chemicals on breast composition in cohort of teenage girls in Santiago, Chile
- **ELLA outreach database** helps with dissemination of messages to nationwide network of BCERP researchers and breast cancer advocacy and environmental health organizations

## ELLA Community Blog

### Menopause and breast cancer: a City of Hope study



Researchers at City of Hope are investigating the influence of hormone-mimicking chemicals during sensitive stage in women's lives. Approximately 30 percent of breast cancers are diagnosed during menopause, a stage in life marked by a decline in the body's production of estrogen and progesterone. Growing evidence suggests it might also be a time when the breast is particularly susceptible

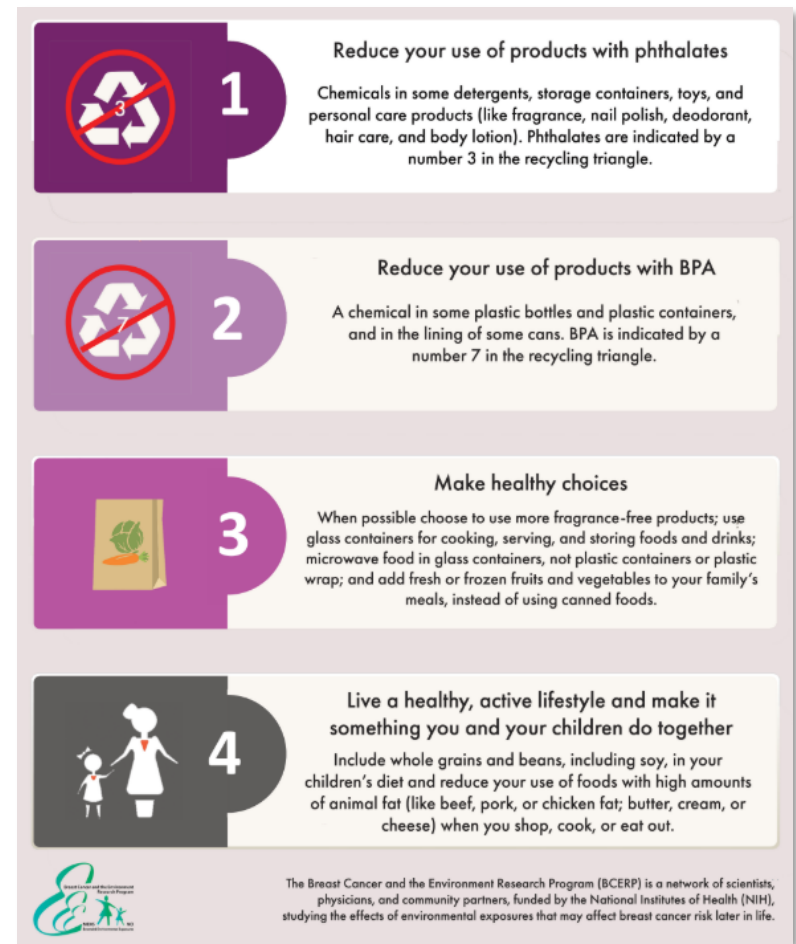
by Silent Spring Institute | June 26, 2019 | Uncategorized | No Comments

[Read more](#)

English-Spanish blog highlights news stories and preventive action tips

# Partnering with “Mommy Bloggers” to Share Breast Cancer Information

- Researchers partnered with 75 “mommy bloggers” to share breast cancer risk messages
- Blog readers who saw and recalled the messages were more likely to:
  - Share the information with their daughters
  - Intend to change their behavior
- Results suggest that **mommy bloggers are important opinion leaders** and are key to disseminating evidence-based risk messages about environmental breast cancer



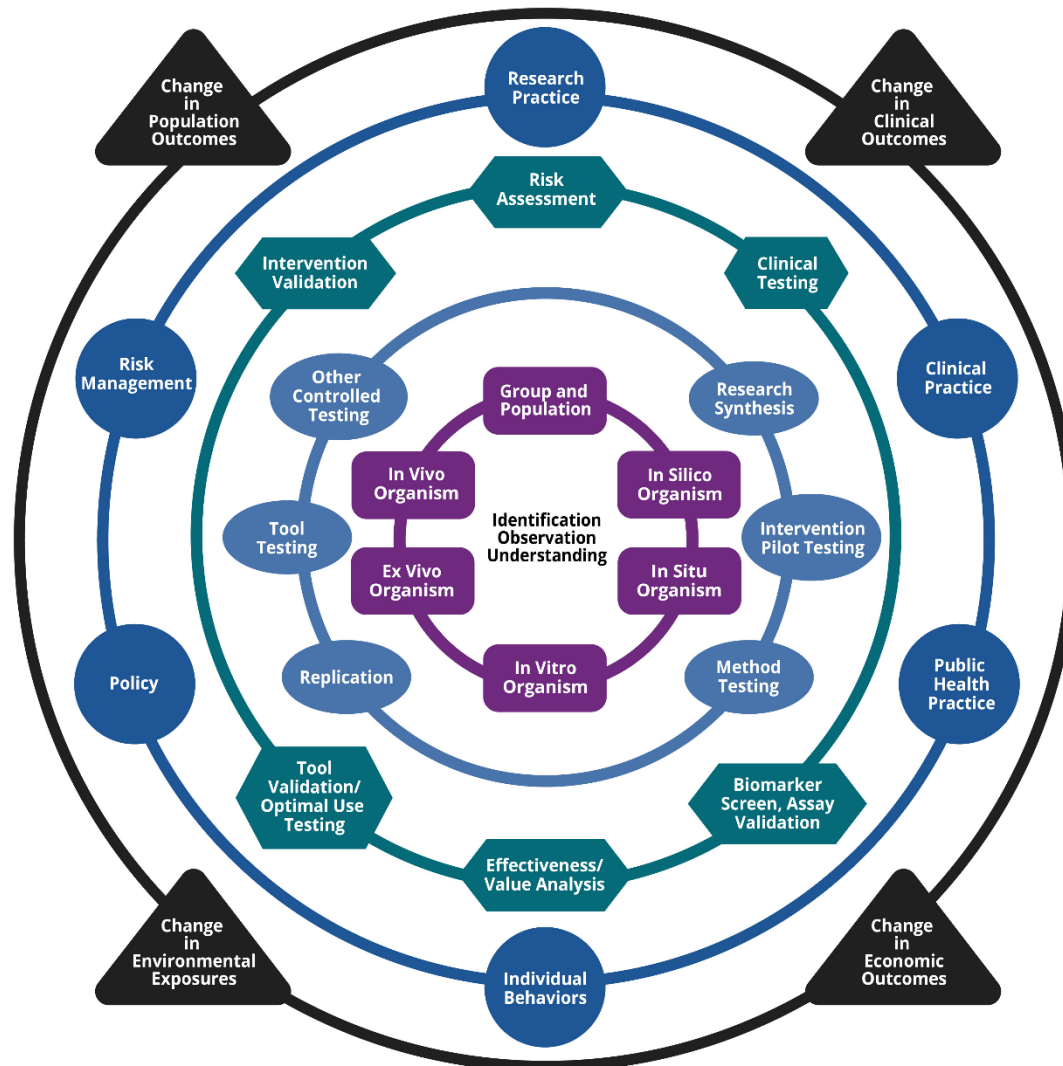


# Continuing Medical Education (CME), an Opportunity for Research Translation

- Health communication researchers and BCERP grantees designed a **CME training** to help healthcare providers **integrate breast cancer research findings** into their everyday clinical practice
- The healthcare providers reported they:
  - Did not routinely discuss breast cancer risk factors with patients
  - Learned that puberty is a vulnerable time for breast cancer risk
  - Acknowledged the importance of addressing breast cancer with patients



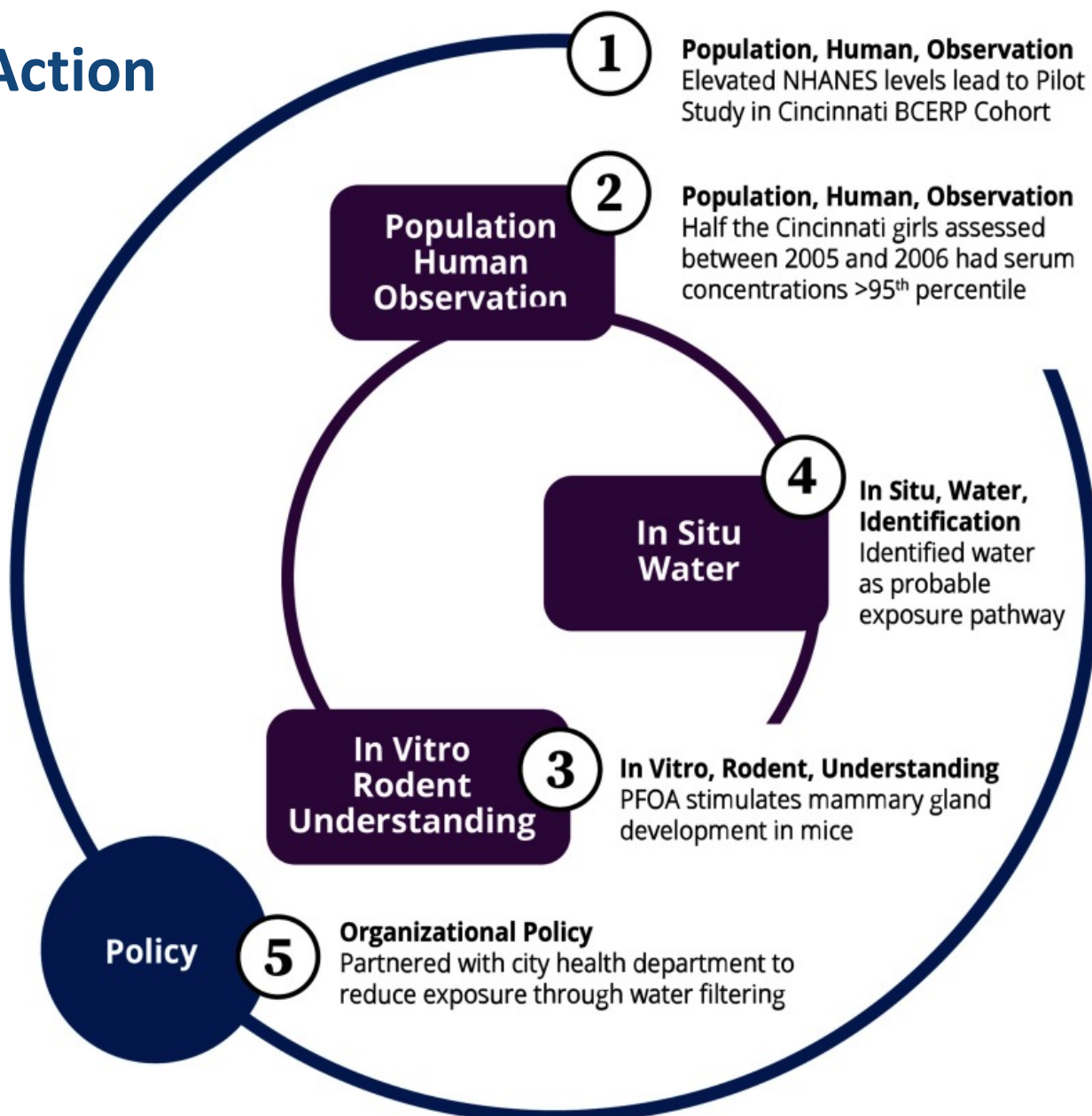
# NIEHS Translational Research Framework



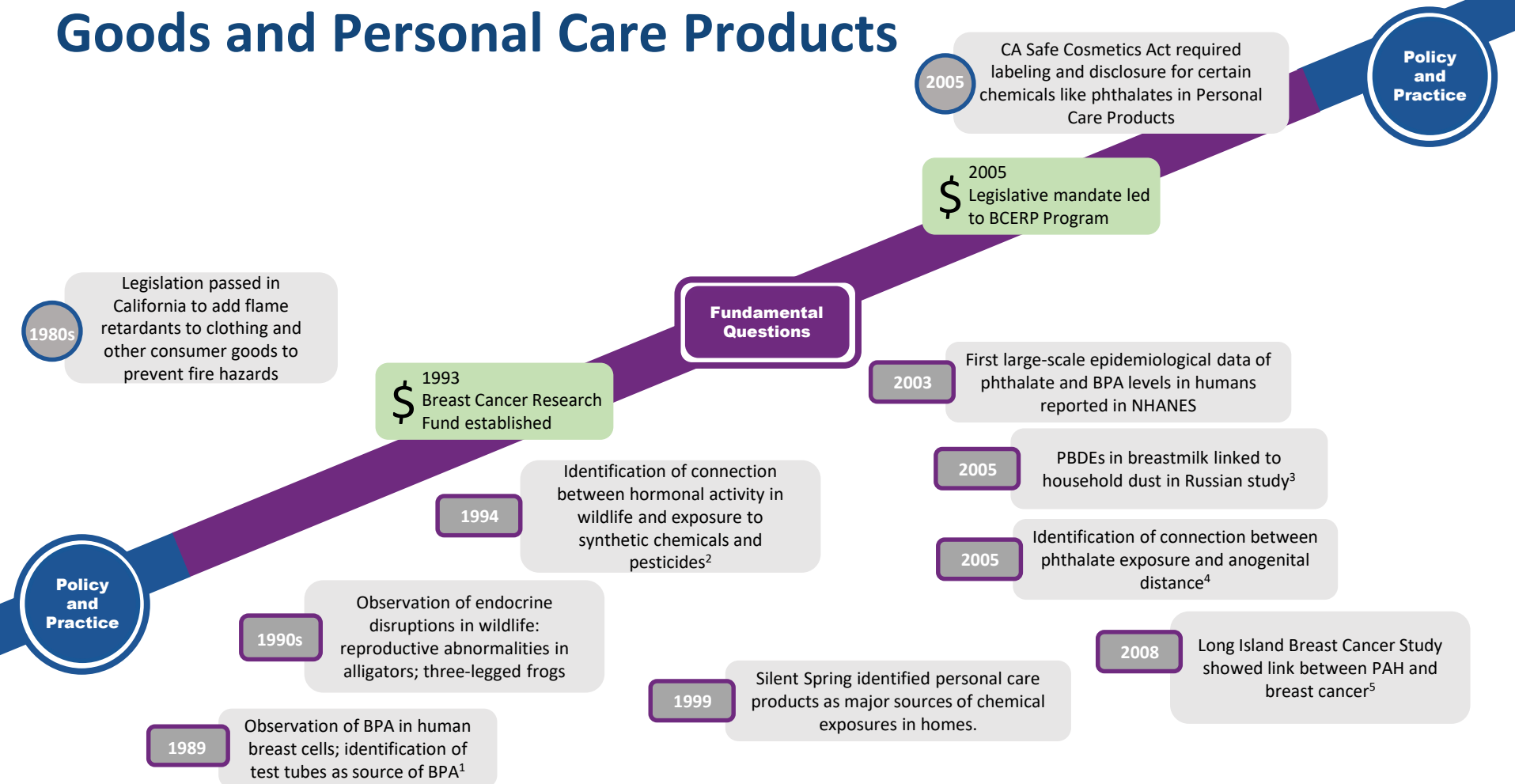


## Example of TRF in Action

Results from pilot study in Cincinnati BCERP cohort led to partnership with city health department to reduce PFAS exposure through water filtering



# Breast Cancer and Chemical Exposure in Consumer Goods and Personal Care Products



## Special Thanks to NIEHS and NCI Partners Over the Years!

### NIEHS

Abee Boyles, Ph.D.  
Jennifer Collins, M.R.  
Caroline Dilworth, Ph.D.  
Christie Drew, Ph.D.  
Symma Finn, Ph.D.  
Elizabeth Maull, Ph.D.  
Kristi Pettibone, Ph.D.  
Leslie Reinlib, Ph.D.  
Thaddeus Schug, Ph.D.  
Claudia Thompson, Ph.D.

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Hayley Aja M.P.H.  
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Armen Ghazarian, Ph.D.  
Nonye Harvey, Dr.P.H.  
Ron Johnson, Ph.D.  
Christie Kaefer, M.B.A.  
Tram Kim Lam, Ph.D.  
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Gila Neta, Ph.D. M.P.P  
Neeraja Sathyamoorthy, Ph.D.  
Debbie Winn, Ph.D.



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# Thank You!

## Any Questions?

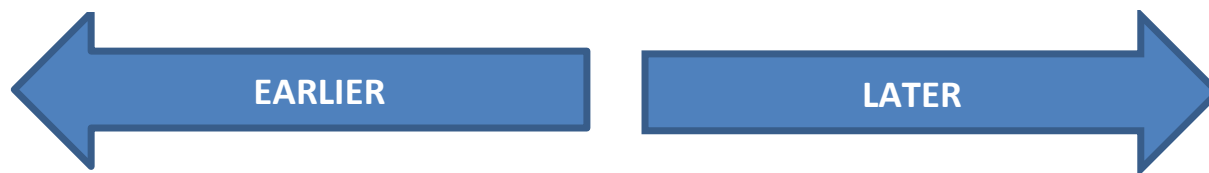






# Additional Slides

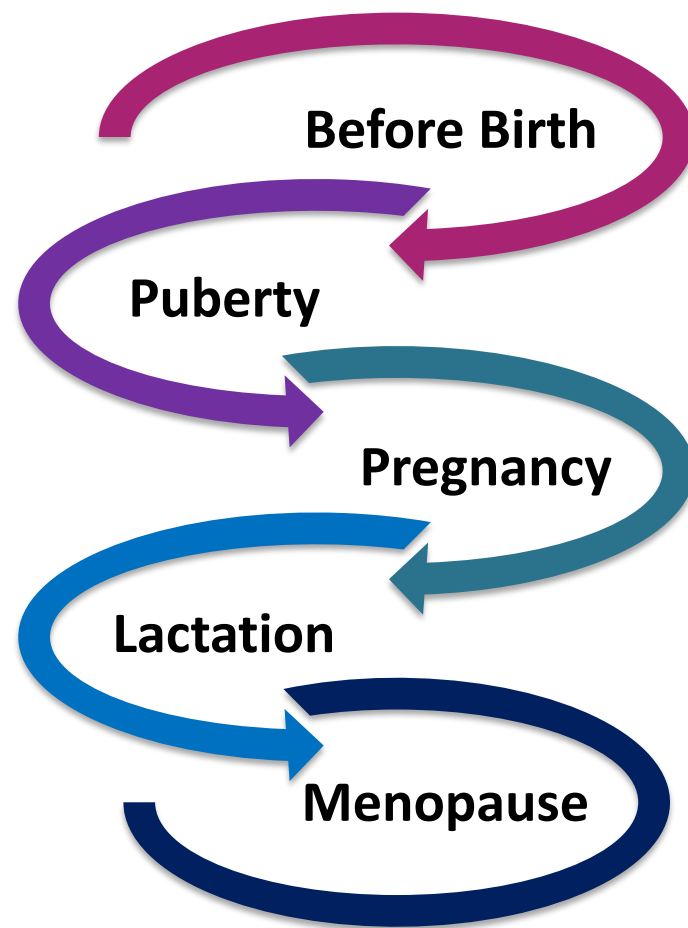
## Impacts on Pubertal Timing

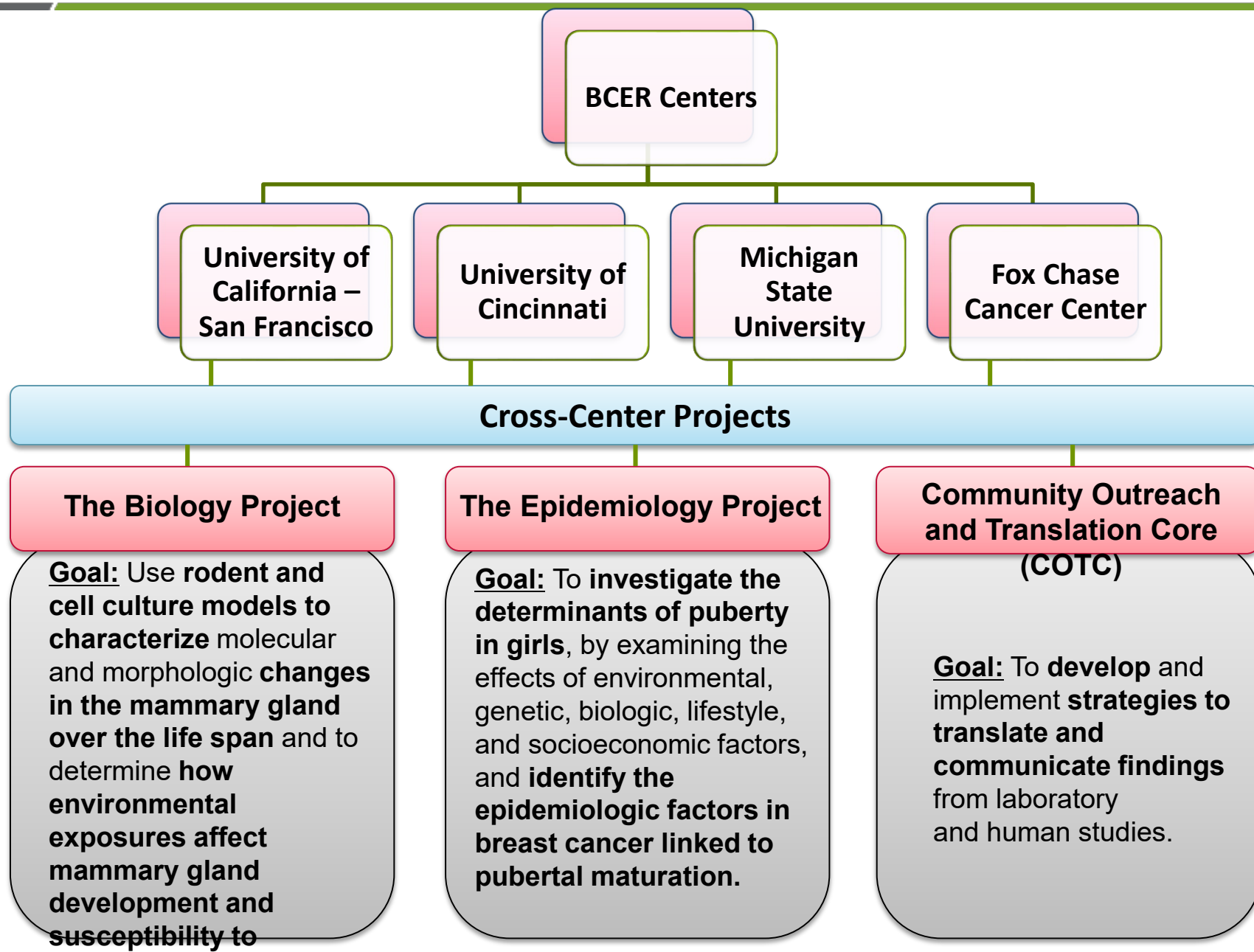


<b>Breast Development</b>	<ul style="list-style-type: none"> <li>• Triclosan and 2,5-dichlorophenol[1]</li> </ul>	<ul style="list-style-type: none"> <li>• Enterolactone and benzophenone-3)[1]</li> <li>• Phytoestrogens (daidzein, genistein, dietary flavonol)[2, 3]</li> </ul>
<b>Pubic Hair Development</b>	<ul style="list-style-type: none"> <li>• Triclosan[4]</li> <li>• Traffic-related air pollution[6]</li> <li>• Prenatal exposure to smoke[7]</li> </ul>	<ul style="list-style-type: none"> <li>• High MWP metabolites[4, 5]</li> </ul>
		<ul style="list-style-type: none"> <li>• POPs(PCBs, OCPs, PBDEs)[8]*</li> </ul>
<b>Menarche</b>	<ul style="list-style-type: none"> <li>• 2,5-dichlorophenol[9]</li> </ul>	<ul style="list-style-type: none"> <li>• Enterolactone and mono-3-carboxypropyl phthalate[9]</li> <li>• Phytoestrogens (dietary flavonol)[10]</li> </ul>
<b>Growth</b>	<ul style="list-style-type: none"> <li>• Low MWP metabolites[11]</li> </ul>	<ul style="list-style-type: none"> <li>• High MWP metabolites[11]**</li> <li>• NIS inhibitors (perchlorate, thiocyanate, nitrate)[12]</li> </ul>

## Breast Cancer Risk and Windows of Susceptibility

- Genetics and family history
- Aging
- Hormonal factors
- High breast tissue density
- Alcohol consumption
- Radiation
- DES
- Obesity
- Other environmental exposures







## BCERP Grantees (Phase II): Windows of Susceptibility



### Prenatal

- Shuk-Mei Ho, Univ. Cincinnati
- Barbara Cohn, PHI and Mary Beth Terry, Columbia



### Prepuberty

- Coral LaMartiniere, Univ. Alabama
- Jose Russo, FCCC
- Tim Huang, Ohio State



### Puberty

- Sandra Haslam, MSU
- Frank Biro, Cincinnati CH
- Lawrence Kushi, Kaiser
- Mary Wolff, Mount Sinai



### Adolescence



### Pregnancy/ Postpartum

- Melissa Troester, UNC



### Menopause

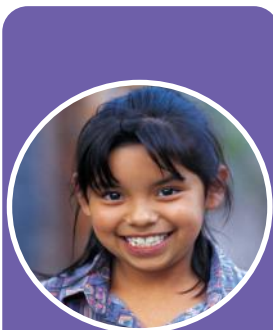
**Life Course Genomics**, Susan Teitelbaum and Jia Chen, Mount Sinai School of Medicine  
**Mammary Gland Architecture across Lifespan**, Zena Werb, UC - San Francisco  
**Genetics of Breast Cancer Risk**, Michael Gould, Univ. Wisconsin

## BCERP Grantees (Phase III): Windows of Susceptibility

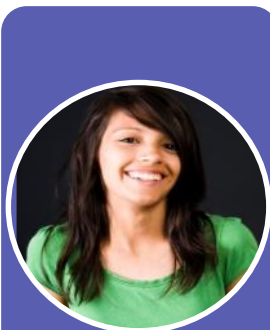


### Prenatal

- Columbia U



### Pre-puberty



### Puberty

- Brigham and Women's Hospital, Silent Spring Institute, Fox Chase Cancer Center, and Univ. of Chile



### Adolescence



### Pregnancy/ Postpartum

- Columbia U
- U Mass, Amherst



### Menopausal Transition

- Beckman Research Institute of the City of Hope

Michigan State University

Georgetown University – Uniformed Services University of the Health Sciences

## BCERP Newsletter

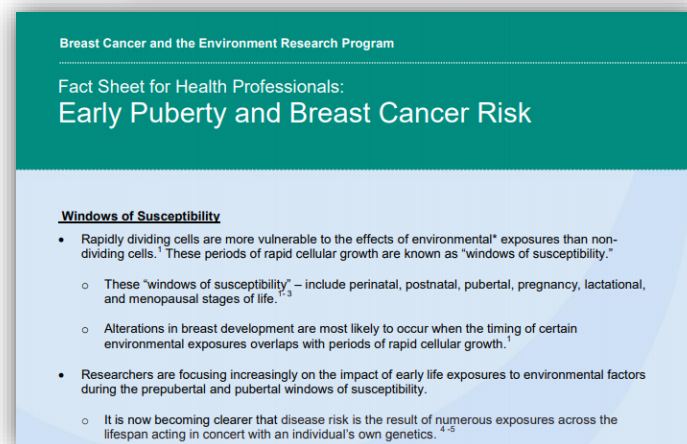
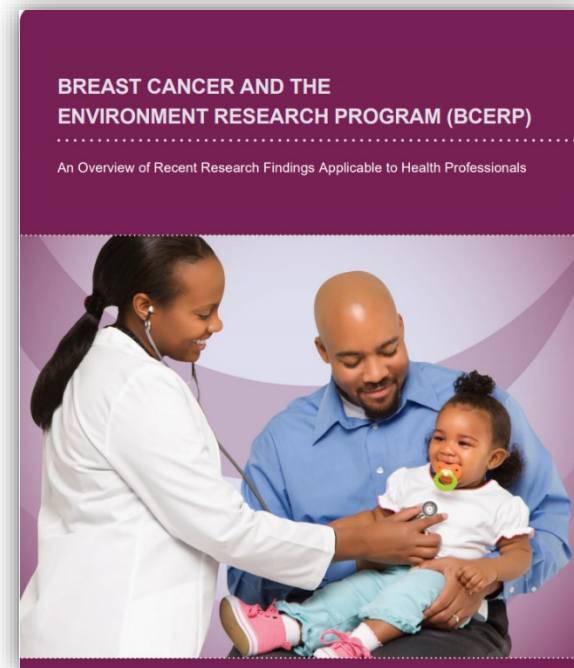
- Keep BCERP researchers and consortium members in the know about:
  - Upcoming meetings and workshops
  - Community outreach activities and highlights
  - Updates to BCERP portal
  - Recent publications
  - Trainee highlights



# BCERP Expanded Toolkit

## Monograph, Brochure, and Fact Sheets for Health Professionals

- Materials for health professionals to guide discussions with female patients and parents
- Share ways to reduce their risk, or their daughters' risk, for developing breast cancer
- Fact sheets on how puberty, lifestyle, and chemicals impact risk





## BCERP Expanded Toolkit

### “Growing Up Female” Coloring Book

- Cincinnati BCERC COTC and breast cancer advocates created coloring book
- Explained different activities involved in the Growing Up Female Study for initial and future study participants
- Adapted for use in other BCERP cohorts, such as CYGNET



## BCERP Scientific Resources Generated

### Cohort of Young Girls' Nutrition, Environment, and Transitions (CYGNET)

- Prospective cohort study of 444 young girls in San Francisco Bay Area
- Examined environmental, lifestyle, and genetic factors in the development of early puberty and other hallmarks of maturation
- Documentation and tracking for biological specimens (blood, urine, saliva/buccal cells)
- Available on the NIEHS-Funded Epidemiology Resources Web Tool



**PI:** Lawrence Kushi, Kaiser Permanente