BREAST CANCER AND THE ENVIRONMENT RESEARCH PROGRAM

13th Annual Meeting

"Understanding the Link between the Environment and Breast Cancer"

November 8-9 2018

Georgetown University Hotel & Conference Center

Washington, DC

SUPPORTED BY

National Institute of Environmental Health Sciences (**NIEHS**)
National Cancer Institute (**NCI**)

Welcome

Welcome to the BCERP Annual Meeting

The overarching goal of the Breast Cancer and the Environment Research Program (BCERP) is to support integrated scientific research to enhance our understanding of environmental and genetic factors underlying breast cancer risk throughout the lifespan, with particular focus on the influence of environmental exposures during time windows of susceptibility. Our Annual Meeting supports this goal by bringing scientists, community partners, breast cancer advocates, and others together to translate research into action to reduce breast cancer.

Special Thanks

The BCERP Annual Meeting Planning Committee offers special thanks to the program co-chairs, Mary Beth Martin, Celia Byrne, and Brenda Richardson, for their extraordinary commitment to facilitating the development of the program for this meeting and to the entire BCERP consortium for attending and sharing their expertise and their valuable contributions to the program.

This BCERP Annual Meeting is supported by grants from the National Institute of Environmental Health Sciences and the National Cancer Institute, including grant U01ES026127 to the University of Wisconsin-Madison to support the Coordinating Center.

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General Information

Registration
The registration table will be open on Thursday, Nov. 8 from 7:00 a.m. – 5:00 p.m., and on Friday, Nov. 9 from 7:30 a.m. – 12:30 p.m.

Meals
Coffee, tea and water will be available during each break.

A buffet lunch will be provided on Thursday, Nov. 8 beginning at 12:15 p.m. in the West Lobby immediately before the two concurrent lunchtime sessions. Please pick up your lunch and head to your respective lunch session as the two lunch sessions will begin promptly.

Poster Information
In the poster session, meeting attendees will present their work and ideas in progress. Presenters will be available to discuss their respective posters during the session in Salon BC on Thursday, Nov. 8. Posters will be eligible for poster awards. Dr. Birnbaum will announce the poster award winners in her closing remarks on Friday, Nov. 9.

Poster presenters are asked to please hang their respective posters between 7:00 a.m.-12:00 p.m. on Thursday, Nov. 8.

Presenters for odd-numbered posters are asked to stand at their posters from 1:45 – 2:30 p.m., and presenters for even-numbered posters are asked to stand at their posters from 2:30 – 3:15 p.m.

We request that posters remain on display through the end of the meeting on Friday, Nov. 9 at 12:30 p.m. They should be promptly removed between 12:30-1:00 p.m.

Wifi
For guests staying at the Georgetown University Hotel and Conference Center and for meeting attendees, wifi is available for free and with no required password on the network Guestnet.

Post Meeting Survey
Please respond to the online survey that will be sent at the conclusion of the meeting so we can make improvements for future meetings.

Next Year
Details will be shared soon regarding the 2019 BCERP Annual Meeting.

Program Committee

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Madison, WI

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Durham, NC

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East Lansing, MI

Amy Trentham-Dietz
University of Wisconsin
Madison, WI

Agenda

Thursday, November 8, 2018

7:00-8:00 a.m. Registration

8:00-8:15 a.m. **Welcome and Introduction of Keynote Speaker – Salon AG**
Local Hosts: Mary Beth Martin, PhD, *Georgetown University*
Celia Byrne, PhD, *Uniformed Services University of the Health Sciences*

Louis M. Weiner, MD, Director, *Georgetown Lombardi Comprehensive Cancer Center*

Craig Shriver, MD, FACS, COL, USA (Ret), Director, *Murtha Cancer Center at Walter Reed National Military Medical Center*

Abee L. Boyles, PhD, Program Director, Population Health Branch, *National Institute of Environmental Health Sciences*

Tram Kim Lam, PhD, MPH, Program Director, Environmental Epidemiology Branch, *National Cancer Institute*

8:15-9:00 a.m. **Keynote Address – Salon AG**
Research directions: the environment, windows of susceptibility, and breast cancer
Deborah M. Winn, PhD, Deputy Director, Division of Cancer Control and Population Sciences, *National Cancer Institute*

9:00-10:30 a.m. **Session 1: Windows of Susceptibility – Salon AG**
Chair: David Salomon, PhD, *National Cancer Institute*

Summary of target cells changes during windows of susceptibility for breast cancer
David Salomon, PhD, *National Cancer Institute*

Environmental exposures during key windows of breast susceptibility
Mary Beth Terry, PhD, *Columbia University*

Effect of pubertal exposure to mixtures on mammary gland gene expression
Julia Santucci-Pereira, PhD, *Fox Chase Cancer Center*

Obesity, progenitor cells, and postmenopausal breast cancer
Lisa Arendt, PhD, *University of Wisconsin*

10:30-10:45 a.m. Break

Thursday, November 8, 2018 *Cont.*

10:45 a.m.-12:15 p.m. **Session 2: Endocrine Disruption and Breast Cancer Risk – Salon AG**
Chair: Joseph Jerry, PhD, *University of Massachusetts Amherst*

Hormone-like effects of metals and metalloids
Mary Beth Martin, PhD, *Georgetown University*

Chemical mixtures from fracking and altered mammary gland development
Laura Vandenberg, PhD, *University of Massachusetts Amherst*

Epigenetic changes in blood as biomarkers of exposure
Susan Neuhausen, PhD, *Beckman Research Institute of City of Hope*

Reporting environmental exposures to study participants and lay people
Julia Brody, PhD, *Silent Spring Institute*

12:15-1:30 p.m. Two concurrent lunchtime sessions are offered. Lunch is provided

Environmental Health Research Opportunities in *All of Us* – Salon AG
Chair: Karin B. Michels, ScD, PhD, *UCLA Fielding School of Public Health*
Speaker: Joni L. Rutter, PhD, Director of Scientific Programs, *All of Us* Research Program, *National Institutes of Health*

NCI Training Opportunities and Career Development – Salon DE
Chair: Richard Schwartz, PhD, *Michigan State University*
Speaker: Jonathan Wiest, PhD, Director, Center for Cancer Training, *National Cancer Institute*

All BCERP meeting attendees are welcome to attend either lunchtime session.

1:45-3:15 p.m. **Poster Session – Salon BC**
Presenters for odd-numbered posters are asked to stand at their posters during 1:45-2:30, and presenters for even-numbered posters are asked to stand at their posters during 2:30-3:15 p.m.

3:15-3:30 p.m. Break

3:30-5:00 p.m. **Session 3: New Emerging Concepts of Environmental Exposures and Risk of Developing Breast Cancer – Salon AG**
Chair: Celia Byrne, PhD, *Uniformed Services University of the Health Sciences*

Abstracts provided on pages 11-14

Serum concentrations of persistent organic pollutants (POPs) and mammographic breast density in a highly exposed population in Triana, Alabama
Hristina Denic-Roberts, MS, RN, *Uniformed Services University of the Health Sciences and Henry M. Jackson Foundation for the Advancement of Military Medicine*

Paternal environmental exposures in the pre-conception window and programming of breast cancer in daughters
Sonia de Assis, PhD, *Georgetown Lombardi Comprehensive Cancer Center*

Thursday, November 8, 2018 *Cont.*

3:30-5:00 p.m. **Session 3: New Emerging Concepts of Environmental Exposures and Risk of Developing Breast Cancer – Salon AG *Cont.***

Xenoestrogens cause estrogen receptor-dependent R-loop formation and DNA damage
Prabin Dhangada Majhi, PhD, *University of Massachusetts Amherst*

Elucidating the effects of polybrominated diphenyl ether (PBDE) on mouse mammary glands through single-cell RNA sequencing analysis
Shiuan Chen, PhD, *Beckman Research Institute of City of Hope*

5:30 p.m. Shuttle bus leaves the Georgetown Conference Center for the Community Forum

6:30-8:30 p.m. **Community Forum – Thurgood Marshall Academy Public Charter School**
2427 Martin Luther King, Jr. Avenue, SE, Washington, DC 20020

In conjunction with the BCERP Annual Meeting, Dr. Linda Birnbaum, Director of NIEHS, will host a Community Forum for the public. Attendees at the BCERP Annual Meeting are welcome to attend the Forum. A shuttle bus will provide transportation between the Georgetown Conference Center and the Community Forum, leaving the Conference Center at 5:30 p.m. and returning around 9:15 p.m.

Friday, November 9, 2018

7:30-8:30 a.m. Registration

8:30-10:00 a.m. **Session 4: Breast Cancer and Environmental Exposures Beyond Classical Endocrine Disrupting Chemicals – Salon AG**
Chair: Richard Schwartz, PhD, *Michigan State University*

The interaction of lifestyle with a putative EDC: high fat diet and BP-3
Richard Schwartz, PhD, *Michigan State University*

Social isolation and breast cancer recurrence
Leena Hilakivi-Clarke, PhD, *Georgetown University*

Air pollution exposures and breast cancer risk
Francine Laden, ScD, *Harvard T.H. Chan School of Public Health*

Challenges to increase diverse engagement in environmental health and breast cancer advocacy
Karen Miller, *Huntington Breast Cancer Coalition*

10:00-10:15 a.m. Break

Friday, November 9, 2018 *Cont.*

10:15-11:45 a.m. **Session 5: Optimal Community Approaches for Environmental Research – Salon AG**
Chair: Lucile Adams-Campbell, PhD, *Georgetown University*

A community-based navigator approach to BCERP: utilizing outreach and engagement
Lucile Adams-Campbell, PhD, *Georgetown University*

Using targeted social media to communicate culturally sensitive and interactive environmental risk information about breast cancer to mothers
Kevin Wright, PhD, *George Mason University*

The Health and Environmental Research in Make-up of Salinas Adolescents (HERMOSA) Study
Kim Harley, PhD, *University of California Berkeley*

Development of a data visualization tool to explore occupational chemical exposures among working California women
Peggy Reynolds, PhD, *University of California San Francisco*

11:45 a.m.-12:30 p.m. **Announcement of Poster Awards and Closing Remarks - Salon AG**
Linda S. Birnbaum, Ph.D, D.A.B.T., A.T.S., Director, *National Institute of Environmental Health Sciences and the National Toxicology Program*

12:30 p.m. Meeting Adjourned

Research Opportunities Lunch Seminar

Breast Cancer and the Environment Research Program (BCERP)

Environmental Health Research Opportunities in *All of Us*

Thursday, Nov. 8, 2018 at 12:15-1:30 p.m.
Salon AG

Featured Speaker

Dr. Joni L. Rutter

Director of Scientific Programs
All of Us Research Program
National Institutes of Health

Join us for a seminar to learn about opportunities for the *All of Us* Research Program to address research on breast cancer and the environment.

Chair: Karin B. Michels, ScD, PhD, UCLA Fielding School of Public Health

Lunch will be provided.

This session is open to any attendees registered for the 13th Annual Breast Cancer and the Environment Research Program (BCERP) Meeting: Understanding the Link between the Environment and Breast Cancer, Georgetown University Hotel & Conference Center
3800 Reservoir Rd NW, Washington, DC 20057

This meeting is open to the public,
community advocates, and researchers at no cost.

GEORGETOWN UNIVERSITY
Georgetown University Medical Center

Hosted by Georgetown University

Conference jointly supported by the National Institute of Environmental Health Sciences (NIEHS) and the National Cancer Institute (NCI), and coordinated by the University of Wisconsin-Madison

Professional Development Lunch Seminar

Breast Cancer and the Environment Research Program (BCERP) Professional Development Seminar for all BCERP Annual Meeting attendees

NCI Training Opportunities and Career Development

Thursday, Nov. 8, 2018 at 12:15-1:30 p.m. - Salon DE

Featured Speaker

Dr. Jonathan Wiest

Director, Center for Cancer Training
National Cancer Institute

Join us for a seminar to learn about the training opportunities provided by the National Cancer Institute and the success of these trainees. Our speaker will describe the various types of funding for training available through NCI.

Chair: Richard Schwartz, PhD, Michigan State University

This session is open to any attendees registered for the 13th Annual Breast Cancer and the Environment Research Program (BCERP) Meeting: Understanding the Link between the Environment and Breast Cancer, Georgetown University Hotel & Conference Center 3800 Reservoir Rd NW, Washington, DC 20057. This meeting is open to the public, community advocates, and researchers at no cost.

Lunch will be provided.

Visit **www.bcerp.org** for more information.

Hosted by Georgetown University

Conference jointly supported by the National Institute of Environmental Health Sciences (NIEHS) and the National Cancer Institute (NCI), and coordinated by the University of Wisconsin-Madison

GEORGETOWN UNIVERSITY
Georgetown University Medical Center

Serum concentrations of persistent organic pollutants (POPs) and mammographic breast density in a highly exposed population in Triana, Alabama

Authors: Rusiecki JA, Denic-Roberts H, Byrne C, Brinton LA, Zahm SH, Mason T, Bonner MA, Blair A, Hoover RN
Presenter: Hristina Denic-Roberts, Uniformed Services University of the Health Sciences

While reported associations between exposure to POPs and breast cancer have been inconsistent, studies of early life exposures suggest a positive association. To further clarify the role of POPs in breast cancer etiology, we conducted a cross-sectional study evaluating serum POPs levels and mammographic density, a strong biomarker of breast cancer risk, among predominantly African American women from Triana, AL, an area highly exposed to dichlorodiphenyltrichloroethane (DDT) from the Tennessee River.

We measured percent breast density (PBD) and lipid-corrected serum concentrations of polychlorinated biphenyls (PCBs) and persistent pesticides: p,p'-DDT, p,p'- dichlorodiphenyldichloroethylene (p,p'-DDE), beta hexachlorocyclohexane (β-HCCH), heptachlor epoxide (h.epoxide), mirex, oxychlordane, and trans-nonachlor, in 210 women. Using partial Spearman correlations (rs), we assessed associations between PBD and each POP. We estimated adjusted mean (95% CI) PBD by tertile of each chemical from linear regression models. We conducted separate analyses among non-users of post-menopausal hormones (PMH) and stratified analyses by age (19-40, 41-54, 55-91 yrs) and age of POPs exposure (<18, 18+ yrs).

Individual, grouped, and total PCBs (∑PCBs) were positively associated with PBD. Associations were stronger and largely statistically significant after excluding current PMH users (rs ∑PCBs =0.17, p=0.03) and among those exposed before age 18 during the heaviest chemical contamination period in Triana (1947-85) (rs ∑PCBs =0.20, p=0.06). Associations between persistent pesticides and PBD were largely null, but among older women not using PMH there was evidence of inverse associations (e.g. rs= -0.26, p=0.07 for β-HCCH). PBD correlated positively with h.epoxide (rs=0.17, p=0.10), mirex (rs=0.18, p=0.09), oxychlordane (rs=0.24, p=0.02), and trans-nonachlor (rs=0.24, p=0.02) among women exposed before age 18 during the heaviest contamination period, but not among those exposed at age 18+. We observed similar patterns in regression analyses.

In our study, higher levels of PCBs, h.epoxide, mirex, oxychlordane, and trans-nonachlor were associated with higher PBD, particularly among the younger women likely exposed in early life, suggesting the importance of timing of exposure.

***Disclaimer:** The views expressed in this abstract are those of the authors and do not necessarily reflect the official views of the Uniformed Services University of the Health Sciences, the Department of Defense, the National Institutes of Health, or the Centers for Disease Control and Prevention.

(Supported by the NIEHS/NCI grant U01ES026132.)

Paternal Environmental Exposures in the Pre-Conception Window and Programming of Breast Cancer in Daughters

Authors: Santana R, Carney EJ, Clarke J, Cao H, Cruz MI, Jin L, Wang Y, de Assis S
Presenter: Sonia de Assis, Lombardi Comprehensive Cancer Center-Georgetown University

Each parent contributes half of their genome to their offspring, but at conception they also transmit a molecular memory of past environmental experiences to their progeny through epigenetic mechanisms. Epidemiologic and animal studies have shown that maternal factors in pregnancy affects offspring's breast cancer risk. Our findings, in a mouse model, suggest a role for paternal pre-conception exposures on their progeny's risk of this disease, using either a dietary (low-protein (LP) intake) or an environmental toxicant (DDT) exposure. In the first study, we found that paternal malnutrition (LP) alters the sperm non-coding RNAs content and expression and increases carcinogen-induced breast cancer rates in daughters. This increase risk was associated with a lower birth weight and alterations in miRNA expression patterns in normal breast tissue and tumors in offspring. Some of those miRNAs have been experimentally shown to regulate the LKB1/AMPK pathway, a central metabolic sensor. Accordingly, we found that both mammary glands and tumors of LP daughters have reduced LKB1/AMPK signaling, with increased mTOR activation in tumors. Their tumors growth faster and are also metabolic programmed with high rates of glutaminolysis compared to controls. In the second ongoing study, we found that paternal DDT exposure also modulates the content and expression of sperm small RNAs. Further, DDT offspring are born smaller and have lower body weight up to 6 weeks of age. DDT female, but not male, offspring show impaired glucose tolerance compared to controls. We also found that DDT daughters have altered mammary gland development and faster growing tumors compared to controls. Strikingly, both DDT and LP exposures have similar impact on the expression of several paternal sperm miRNAs (e.g. miR-10b, miR-30d) compared to controls, suggesting a common underlying mechanism. Several phenotypic similarities were also observed in offspring of DDT and LP fathers, including low birth weight, metabolic dysfunction, altered mammary gland development and increased mammary tumor growth. Our study offers some insights on how the paternal pre-conception window can play a role on offspring's breast cancer predisposition. Whether our findings hold true in humans still needs to be elucidated.

(Supported by Prevent Cancer Foundation (Research grant # 299045 to S de Assis.), The American Cancer Society (Research Scholar Grant to S. de Assis.), the National Institutes of Health (1P30-CA51008 andTL1TR001431).)

Xenoestrogens cause estrogen receptor-dependent R-loop formation and DNA damage

Authors: Majhi PD, Sharma A, Dunphy KA, Roberts AL, Daniele EA, Schneider SS, and Jerry DJ
Presenter: Prabin Dhangada Majhi, University of Massachusetts Amherst

Abstract: Xenoestrogens (XE2) are chemicals, which interact with estrogen receptors (ER) to mimic or interfere with the effect of estrogen (E2). While the effects of the XE2 are not well established, high serum estrogen level is known to increase the relative risk of breast cancer by 1.4 - 6.4 fold in post-menopausal women (Brown, 2015). Recent studies show E2 induced transactivation accumulate DNA:RNA hybrids (R-loops), a potential site for DNA double strand breaks (DSBs), in the genome (Stork, 2016). Thus, our hypothesis is to determine whether XE2 stimulate transcriptional response and induce DNA damage similar to E2.

Methods: In our study, T47D cell line which expresses both ER√é¬± and ER√é¬≤ was exposed to physiologic range of XE2 concentrations, e.g., benzophenone-3 (BP-3) [0.5-50µM] and propyl paraben (PP) [0.5-10µM] with or without ER-antagonist ICI (1µM) for 24 hours. Exposure to √é‚Ä¢2 (17√é¬≤-estradiol) [0.5-100nM] was used as a positive control. Transcriptional responses were quantified using an integrated ERE-luciferase reporter and qPCR for endogenous genes. Proliferation was monitored using the Alamar Blue assay. DNA damage was determined using γ-H2AX immunofluorescence. R-loops were detected using the S9.6 antibody against DNA-RNA hybrids in the genome. Acute treatment of ovariectomised mice with E2, BP3 or PP was for 4-days.

Results: We demonstrated PP [1-30µM] and BP3 [1-30 µM] cause dose-dependent increase in DSBs as determined by γ- H2AX foci similar to E2[1-100nM]. R-loop accumulation was observed in the treatments with showing DSBs. Adding ICI to the treatment condition abrogated both R-loop and γ-H2AX foci. However, PP induced expression of estrogen-responsive genes (AREG and PGR) only at 10 µM, whereas BP3 [10 µM] has modest effect on transactivation of PGR. Induction of AREG and PGR was observed at 0.5 nM E2. Consistent with the transcriptional response, proliferation studies determined that E2 [0.5 nM] showed highest proliferation followed by PP [10 µM]. However, BP3 [50 µM] showed no increase in proliferation. We also demonstrated that, acute exposure to PP and BP3 show significant accumulation of R-loop in mouse mammary epithelia, similar to E2 exposure.

Conclusion: Acute exposure to XE2 (PP and BP3) is sufficient to induce ER-mediated DNA damage via R-loop at concentration 10 fold lower than that is required for transactivation. The near universality of exposure to both of these PP and BP3 (Ye, 2006; Woodruff 2011) implies that a substantial fraction of the population is at risk of the deleterious estrogenic response such as DNA damage.

(Supported by grants from National Institutes of Health U01ES026140.)

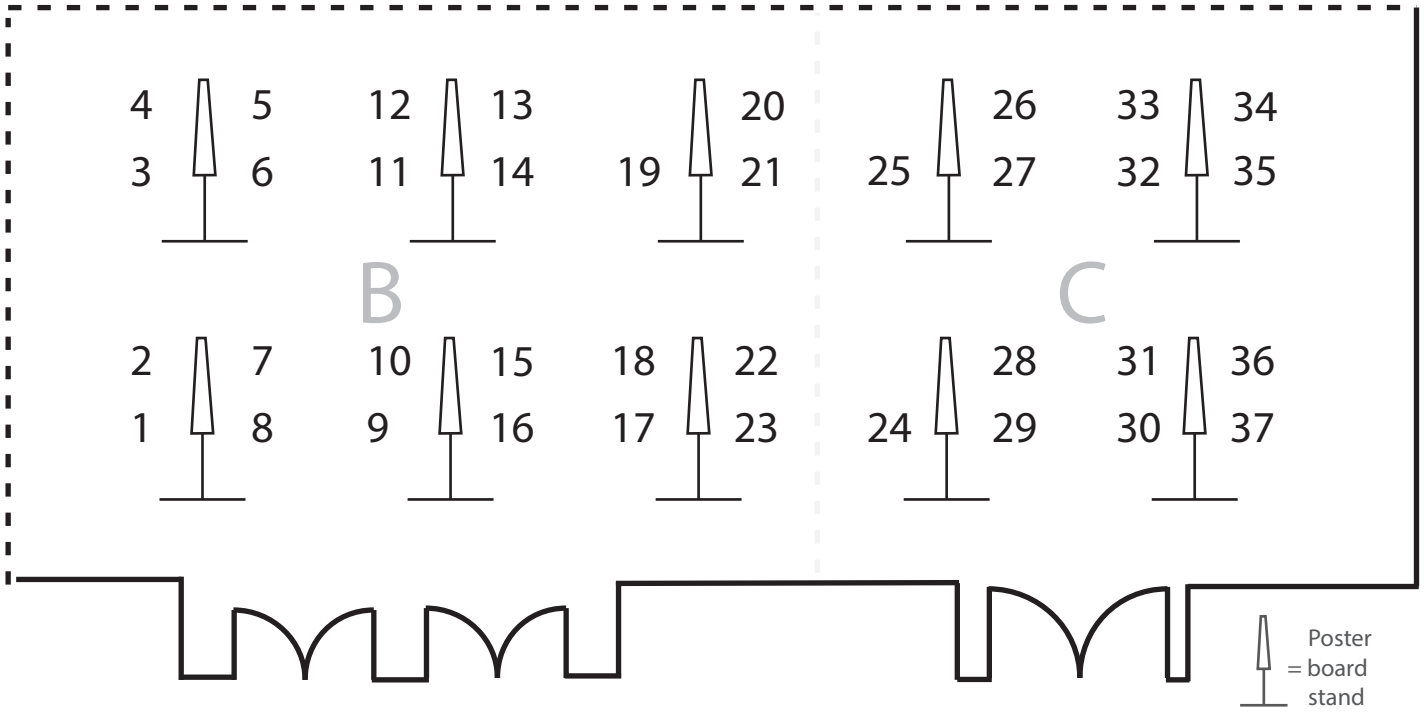
Elucidating the effects of Polybrominated Diphenyl Ether (PBDE) on mouse mammary glands through single-cell RNA sequencing analysis

Authors: Kanaya N, Chang G, Wu X, Bernal L, Wang J, Warden C, Yamamoto T, Li J, Park JS, Synold TW, Neuhausen SL, and Chen S
Presenter: Shiuan Chen, Beckman Research Institute of City of Hope

Polybrominated Diphenyl Ethers (PBDEs) have been used as flame retardants in household materials. Their environmental persistence has led to continuous human exposure at significant concentrationsin tissues. PBDEs are thought to be endocrine disrupting chemicals and are associated with a variety adverse health effects. Yet, the relationship between breast cancer risk and the biological activity of PBDEs in the mammary glands is poorly understood. Since BDE-47, BDE-100 and BDE-153 are three major PBDE congeners in human serum, we examined the in vivo effects of these PBDEs using ovariectomized mice, a surgical menopause model. In the presence of physiologically-relevant dosage of 17β-estradiol (E2), PBDE-treated mouse mammary glands exhibited a large number of terminal end bud-like structures with multicellular layered structures and Ki67-positive cells. RNA-sequencing results suggest that PBDEs augment the estrogen-mediated cell proliferation and modulate immune regulation in mammary glands. In order to elucidate the effects of PBDEs on different cell types, single-cell RNA sequencing (scRNA-seq) analysis has been performed. We digested the mammary glands from control (vehicle), E2, or E2+PBDE treated mice into single cells. All samples were prepared for scRNA-seq using 10x Genomics platform. Our results revealed that PBDE increased the number of ER+/PR+ and ER-/PR+ cells in two luminal epithelial populations (hormone-responsive/mature luminal and secretory/luminal progenitor). Furthermore, E2 and PBDE treatments increased c-Kit+ cells. Moreover, the M2 macrophage population was increased, suggesting cross talk between immune cells and epithelial cells. Our results can potentially advance our understanding of, at the single cell level, how PBDE exposure during menopausal transition can modify mammary gland structure and increase the risk of developing breast cancer.

(Supported by the NIEHS/NCI grant U01ES026137.)

Poster Session Map



Environmental Exposures in Relation to Breast Cancer (Posters #1-12)

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Mechanisms of Breast Cancer Development (Posters #20-24)

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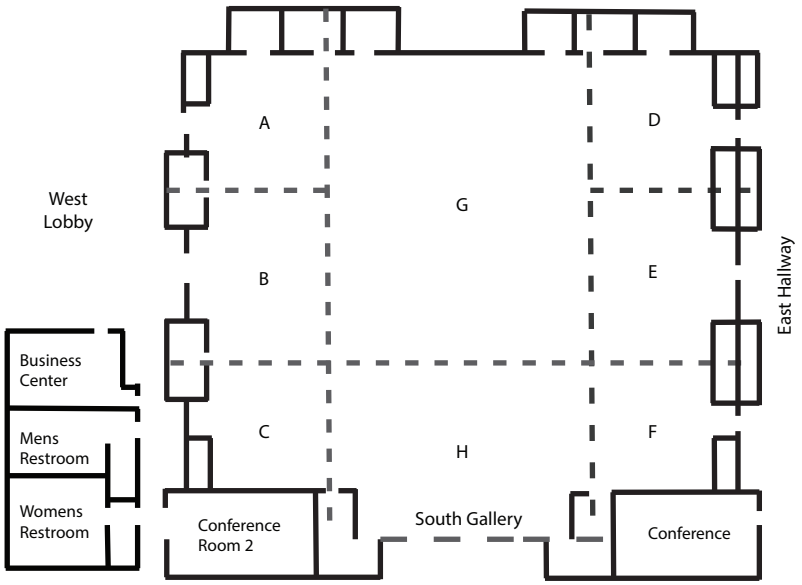
BCERP Annual Meeting Room Map



Posters

Environmental Exposures in Relation to Breast Cancer (#1-12)

Poster #	Presenter	Title
1	Richard Schwartz	BP3 during puberty alter gene expression associated with cancer-inflammation-immunity crosstalk in p53-null mammary glands
2	Richard Schwartz	The effect of oxybenzone on tumor growth depends on the high content of dietary saturated animal fat
3	Prabin Dhangada Majhi	Xenoestrogens cause estrogen receptor-dependent R-loop formation and DNA damage
4	John Psaltis	The Role of Metalloestrogens and Anti-estrogens in ERα Activation and Response to Endocrine Therapy
5	Reem Gahtani	Progesterone-independent activation of progesterone receptor (PR) by metal/ metalloid anions
6	Camile Castilho Fontelles	Ancestral paternal obesity: systemic versus local effects on offspring mammary tissue development and tumorigenesis
7	Rebecca Kehm	Prenatal Exposure to Airborne Polycyclic Aromatic Hydrocarbons and Growth and Development in Adolescent Girls
8	Raquel Santana da Cruz	Pre-conception paternal DDT exposure and programming of metabolic dysfunction and breast cancer risk in offspring
9	Fabia de Oliveira Andrade	Genistein prevents activation of mammary tumor immunosuppressive pathways during tamoxifen treatment in rats exposed to obesity-inducing high fat diet in utero
10	Heng-Hong Li	Assessment of estradiol and endocrine disruptors induced transcriptomic responses
11	Kerrie Briggs Bouker	In utero exposure to ethinyl estradiol predisposes to the development of mammary tumors with an aggressive/endocrine resistant phenotype
12	Yuan Chun Ding	Association of PBDEs and BPA and epigenome modulation in sera of women at the menopausal transition

Communication Science (#13)

Poster #	Presenter	Title
13	Kami J Silk	Comparing Caregivers' Perceived Risk of Breast and Skin Cancer for Children: Implications for Breast Cancer and Environment Risk Communication

Community Outreach and Dissemination (#14-18)

Poster #	Presenter	Title
14	Kami J Silk	Lay perceptions of breast density and breast cancer risk
15	Nur Zeinomar	Empowering youth in cancer risk reduction through education: preliminary findings

Community Outreach and Dissemination (#14-18) *Cont.*

Poster #	Presenter	Title
16	Sara Frawley, Sam Roberts	Exploring glyphosate-based herbicide effects on liver gene expression in rats and assessing knowledge of pesticides in Long Island communities
17	Raymond Lin	To Replace Toxins Linked with Breast Cancer: Applications of Sophorolipid Butyl Ester in the Stabilization of O/W Emulsions for a Novel Food Packaging Material
18	Michele Rakoff	Engaging community members to accelerate translational research on breast cancer and the environment

Breast Density (#19)

Poster #	Presenter	Title
19	Shaoqi Fan	Relationship of epithelial nuclear density with measures of terminal ductal lobular unit involution and mammographic density

Mechanisms of Breast Cancer Development (#20-24)

Poster #	Presenter	Title
20	Gai Yan	Progesterone Receptor Activation by Metallohormones
21	Andrea R Hindman	Prioritizing Breast Cancer Susceptibility from Early-Life Chemical Exposures in Toxicity Testing
22	Debashish Sahay	Prenatal and pregnancy PAH alter DNA methylation in breast cancer genes belonging to AHR/ARNT/AHRR pathway
23	Sallie Schneider	Benzophenone-3 (BP3) exposure increases TGF-β expression in mouse and human mammary tissues
24	Gregory Chang	Elucidating the effects of Polybrominated Diphenyl Ether (PBDE) on mouse mammary glands through single-cell RNA sequencing analysis

Windows of Susceptibility (#25-29)

Poster #	Presenter	Title
25	Hafsa Gurdogan	The effects of pubertal exposure to benzyl butyl phthalate (BBP), perfluorooctanoic acid (PFOA), and zeranol on the uterus and the serum levels of estrogen and progesterone in the female Sprague-Dawley rats
26	Peter Salim Khouri, Jedediah Bondy, Nicolas Cormier, Amber Zafar	Pubertal exposure to perfluorooctanoic acid (PFOA), butyl-benzyl phthalate (BBP), and zeranol do not affect the expression of estrogen receptor in the Sprague-Dawley rat's mammary gland.
27	Julia Santucci-Pereira	Pubertal exposure to PFOA and zeranol induces gene expression changes in the mammary gland of Sprague-Dawley rats
28	Francesca Scotto, Matthew Erlich	Impact of pubertal exposure to BBP, PFOA, or zeranol, alone or in combination, on the proliferative activity of the mammary gland of Sprague-Dawley rats.

Windows of Susceptibility (#25-29) *Cont.*

Poster #	Presenter	Title
29	Amanda Shirazi, Isobelle Lim	Effects of perinatal exposures to propylparaben, an estrogenic chemical, on mammary gland development in the mouse

Other (#30-37)

Poster #	Presenter	Title
30	Nur Zeinomar	Airborne PAH and long term body size in a cohort of African American and Hispanic women in Northern Manhattan
31	Omonefe Omofuma	Meat and fish preparation methods and risk of breast cancer by estrogen receptor status in the Carolina Breast Cancer Study (CBCS)
32	Carmela Veneroso	Inflammatory Breast Cancer in a husband and wife: The importance of environmental triggers
33	Vanessa De La Rosa	Mining high-throughput in vitro testing data to inform in vivo studies of BCERP chemicals
34	Sivanesan Dakshanamurthy	Prediction of Acute Toxicity and Carcinogenicity of Chemicals using Machine Learning Model
35	Jennifer Elizabeth Bird	Applying Network Analysis to Understand Trends in Collaboration within the Breast Cancer and Environment Research Program (BCERP) Consortium
36	Cecily Fassler	Perfluorooctanoate and Insulin Resistance in Young Girls in Greater Cincinnati
37	Olena Morozova	Effects of high fat diet and oxybenzone on tumor vascularity

Environmental Exposures in relation to Breast Cancer

#1: BP3 during puberty alter gene expression associated with cancer-inflammation-immunity crosstalk in p53-null mammary glands

Xie F, Haslam SZ, Schwartz RC

Purpose: We previously showed that a diet high in animal fat (HFD) at either puberty or adulthood in the absence of obesity promotes mammary tumorigenesis in a p53-null transplant BALB/c mouse model. We found that the putative endocrine disrupting chemical benzophenone-3 (BP3, a common ingredient in sunscreen) stimulates mammary epithelial proliferation at puberty in mice fed HFD. These results led us to examine how BP3 might affect HFD promotion of mammary tumorigenesis.
Methods: p53-null mammary gland-transplanted BALB/c mice were fed the following diets with or without BP3 from 3 to 13 weeks and 3 to 26 weeks of age: low fat diet (L, 10% kcal fat); L switched to HFD at 10 weeks of age (L-H); HFD switched to L at 10 weeks of age (H-L). At 13 and 26 weeks, inguinal mammary glands were excised, lymph nodes removed and mammary gland RNAs analyzed using mouse cancer inflammation and immunity crosstalk PCR arrays. We also collected and identified p53-null generated tumors (epithelial and spindle) from each dietary group.
Results: At 13 weeks, mice fed H-L showed BP3-induced increases in mammary gland expression of Ccl5, Csf1, Pd-L1, Egfr, Hif1a, Gbp2b and Bcl2l1, but BP3 only increased Egfr, Gbp2b and Bcl2l1 in mice fed L-H. In contrast, mice fed L showed BP3-induced decreases in Tlr4 and KitL; expression of other genes was unaltered. At 26 weeks, BP3 increased Vegfa expression in mice fed L, but decreased Vegfa in mice fed H-L; BP3 also increased Kitl in mice fed L. Both epithelial and spindle tumors were identified by H&E staining. More BP3 regulated genes were identified in epithelial than in spindle tumors in both L and H-L diets. Interestingly, in epithelial tumors, BP3 increased Bcl2l1 in mice fed L, while Bcl2l1 was decreased in mice fed H-L. Foxp3 and Hif1a were increased in both L and H-L diets. Genes such as IL15, IL4, IL10 were only increased in mice fed L, while IL4 and IL13 were only increased in mice fed H-L.
Conclusions: Gene expression related to macrophage polarization and tumorigenesis was increased in mammary glands of H-L+BP3 mice at 13 weeks compared to mice on other diets. Different patterns of gene expression involving fewer genes were observed at 26 weeks and in tumors. The data suggest diet, life stage, and tissue-specific BP3 effects.

(Supported by the NIEHS/NCI grant U01 ES026119.)

#2: The effect of oxybenzone on tumor growth depends on the high content of dietary saturated animal fat

Kariagina AY, Borin MA, Haslam SZ, Schwartz RC

Purpose: Oxybenzone or benzophenone-3 (BP-3), a common ingredient of North American sunscreens, is a putative endocrine disrupting chemical and we have shown it to exhibit estrogen-like proliferative activity in normal mouse mammary gland. The purpose of the current study was to investigate whether BP-3 influences tumor growth in mammary transplants of Trp53-null tissue.
Methods: Rudimentary mammary ductal trees were surgically removed from the inguinal glands of three-week-old BALB/c mice and Trp53-null mammary tissue was transplanted into these cleared fat pads. Mice were fed a low fat diet (LFD; 10% kcal fat) or a diet high in saturated animal fat diet (HFD; 60% kcal fat) only during puberty or only after puberty (HFD-LFD or LFD-HFD, respectively). These dietary regimens were based on our previous studies showing that a pubertally restricted HFD had a long-lasting promotional effect on tumorigenesis. Dietary groups were untreated or additionally received BP-3 in their diet (~70 mg/kg body weight/day). Mice were monitored for tumor development and tumors were collected.
Results: Analysis of tumor histopathology revealed two major tumor types, more differentiated epithelial-like and less differentiated spindle cell tumors. For epithelial tumors from mice fed HFD any time throughout their life, BP-3 significantly increased proliferation. Interestingly, BP-3 showed a trend toward increased apoptosis in LFD tumors. HFD given during puberty by itself decreased apoptosis in epithelial tumors. In spindle cell tumors, BP-3 increased proliferation in tumors from all diet groups.

BP-3 also showed a trend toward decreased apoptosis in LFD and HFD-LFD groups. Notably, HFD given in adulthood significantly increased proliferation and decreased apoptosis of spindle cell tumors.
Conclusion: These results indicate that BP-3 promotes proliferation of epithelial tumors in combination with HFD at either puberty or adulthood and spindle cell tumors irrespective of diet. Even on LFD, BP-3 increases proliferation and decreases apoptosis in spindle cell tumors. Altogether, our findings demonstrate that the environmental chemical BP-3 has a promotional effect on tumor growth (with the exception of LFD epithelial tumors) that can be additionally enhanced by the presence of HFD.

(Supported by the NIEHS/NCI grant U01 ES026119.)

#3: Xenoestrogens cause estrogen receptor-dependent R-loop formation and DNA damage

Dhangada Majhi P, Sharma A, Dunphy KA, Roberts AL, Daniele EA, Schneider SS, Jerry DJ

Background: Xenoestrogens (XE2) are chemicals, which interact with estrogen receptors (ER) to mimic or interfere with the effect of estrogen (E2). While the effects of the XE2 are not well established, high serum estrogen level is known to increase the relative risk of breast cancer by 1.4 - 6.4 fold in post-menopausal women (Brown, 2015). Recent studies show E2 induced transactivation accumulate DNA: RNA hybrids (R-loops), a potential site for DNA double strand breaks (DSBs), in the genome (Stork, 2016). Thus, our hypothesis is to determine whether XE2 stimulate transcriptional response and induce DNA damage similar to E2.
Methods: In our study, T47D cell line which expresses both ERα and ERβ was exposed to physiologic range of XE2 concentrations, e.g., benzophenone-3 (BP-3) [0.5-50μM] and propyl paraben (PP) [0.5-10μM] with or without ER-antagonist ICI (1μM) for 24 hours. Exposure to E2 (17β-estradiol) [0.5-100nM] was used as a positive control. Transcriptional responses were quantified using an integrated ERE-luciferase reporter and qPCR for endogenous genes. Proliferation was monitored using the Alamar Blue assay. DNA damage was determined using γ-H2AX immunofluorescence. R-loops were detected using the S9.6 antibody against DNA-RNA hybrids in the genome. Acute treatment of ovariectomised mice with E2, BP3 or PP was for 4-days.
Results: We demonstrated PP [1-30 μM] and BP3 [1-30 μM] cause dose-dependent increase in DSBs as determined by γ-H2AX foci similar to E2[1-100nM]. R-loop accumulation was observed in the treatments with showing DSBs. Adding ICI to the treatment condition abrogated both R-loop and γ-H2AX foci. However, PP induced expression of estrogen-responsive genes (AREG and PGR) only at 10 μM, whereas BP3 [10 μM] has modest effect on transactivation of PGR. Induction of AREG and PGR was observed at 0.5 nM E2. Consistent with the transcriptional response, proliferation studies determined that E2 [0.5 nM] showed highest proliferation followed by PP [10 μM]. However, BP3 [50 μM] showed no increase in proliferation. We also demonstrated that, acute exposure to PP and BP3 show significant accumulation of R-loop in mouse mammary epithelia, similar to E2 exposure.
Conclusion: Acute exposure to XE2 (PP and BP3) is sufficient to induce ER-mediated DNA damage via R-loop at concentration 10 fold lower than that is required for transactivation. The near universality of exposure to both of these PP and BP3 (Ye, 2006; Woodruff 2011) implies that a substantial fraction of the population is at risk of the deleterious estrogenic response such as DNA damage.

(Supported by the NIEHS/NCI grant U01 ES026140.)

#4: The Role of Metalloestrogens and Anti-estrogens in ERα Activation and Response to Endocrine Therapy

Psaltis J, Wang Q, Yan G, Sharawi Z, Cyrus K, Cahalan S, Martin MB

In the United States, a woman has a 12.4%, or a 1-in-8, lifetime risk of being diagnosed with breast cancer at some point in their lifetime. At the time of diagnosis, at least 70% of tumors are classified as ER-positive, yet a third of these tumors develop resistance or fail to respond to endocrine therapy. Although not well understood, mechanisms believed to be responsible for endocrine resistance include hormone independent activation of estrogen receptor –alpha (ERα) due to overexpression, mutation, or activation of growth factor signal transduction pathways.

Since ERα is significant in the etiology, progression and treatment of breast cancer, understanding the mechanisms by which the receptor is activated by environmental estrogens is crucial in formulating more efficient and effective prevention and treatment strategies. Published results from our laboratory show that in MCF7 breast cancer cell lines, metalloestrogens activate ERα. Metalloestrogens refer to metals that activate the estrogen receptor in the absence of estradiol. Bivalent cationic metalloestrogens include metals such as calcium, cadmium, cobalt, copper, nickel, chromium, lead, mercury, and tin. The goal of our research is to determine whether environmental exposure to metalloestrogens contribute to hormone independent and resistance breast cancer by noncompetitively competing with anti-estrogens for binding and consequent activation of ERα. To address this question, we tested the ability of calcium to activate metalloestrogen binding site mutants of ERα (H516A, E523A) in the presence or absence of anti-estrogens. As expected, estradiol activated these mutants and calcium and the anti-estrogens not. Preliminary results further show that calcium plus anti-estrogen failed to activate the E523A ERα mutant, but interestingly, calcium plus tamoxifen activated the H516A mutant, suggesting that metalloestrogens influence anti-estrogen treatment outcomes.

(Supported by the NIEHS/NCI grant U01 ES026132.)

#5: Progesterone-independent activation of progesterone receptor (PR) by metal/ metalloid anions

Gahtani RM, Yan G, Qiaochu W, Cyrus K, Martin MB

Breast cancer is the most common cancer in women and steroid hormones are known to contribute in breast cancer progression. According to the Women's Health Initiative (WHI) and the Million Women Study, progesterone and its synthetic analogs such as MPA significantly contribute to the incidence of breast cancer. Published data from our lab showed that metalloestrogens including metal/metalloid anions (oxoanions) and bivalent cations have estradiol-like activity in breast cancer cell lines that leads to estradiol-independent activation of estrogen receptors (ER). ER and progesterone receptors (PR) are members of the nuclear receptor family and have similar protein structure & function.

In this study, we asked whether metalloestrogens also activate PR. Our preliminary data with T47D-co cells show that oxoanions induce the transcription of PR regulated genes including BIRC3, HSD11B2, FKBP5 and STAT5A. Our preliminary data also show that in the PRB transfected Hek-239T cells oxoanions induce the transcription of BIRC3, FKBP5 and SERPINA5. These preliminary data suggest that metal/metalloid anions (oxoanions) including arsenite, nitrite, selenite and vanadate have progesterone-like activity that mimics progesterone and activates the progesterone receptor independent of its ligand.

(Supported by the NIEHS/NCI grant U01 ES026132.)

#6: Ancestral paternal obesity: systemic versus local effects on offspring mammary tissue development and tumorigenesis

Fontelles CC, Warri A, da Cruz RS, Cruz MI, Barin E, and de Assis S

Background: Obesity and overweight are risk factors for breast cancer, particularly in the post-menopausal years. We recently reported that having a history of ancestral overweight from the paternal lineage is enough to increase breast cancer susceptibility in daughters. Using a mouse model, we demonstrated that paternal consumption of an obesity inducing diet (OID) altered mammary gland development, increased mammary carcinogenesis and disrupted metabolic parameters in the female offspring, compared to the female offspring of fathers who consumed only control (CO) diet. Given both the systemic and local mammary tissue alterations observed, we aimed to investigate in more details why daughters of overweight fathers are at increased risk for breast cancer. More specifically, we used mammary gland transplantation experiments to study whether this ancestrally-induced breast cancer predisposition is linked to systemic factors and/or mammary tissue confined changes in daughters.
Material and methods: Male mice were exposed either to a control (CO) or to high-fat (OID) diet. CO and OID male mice were then mated with female mice fed CO diet exclusively. Female offspring of both CO and OID male mice underwent a mammary gland transplantation surgery. Briefly, female offspring had their mammary fat pad area between the nipple and the proximal lymph node excised.

Afterwards, mammary tissue fragments (1 mm3) of a donor mouse, either CO or OID female offspring, were implanted into a pocket made in the cleared fat pad. The transplantations were performed from CO female offspring donors to both CO [CO (CO)] and OID [OID(CO)] female offspring hosts, as well as from OID female offspring donors to both CO [CO(OID)] and OID [OID(OID)] female offspring hosts. Approximately 10 weeks post-surgery, the mammary glands were collected, photographed and analyzed using ImageJ software to determine branching density, ductal elongation and number of Terminal End Buds. Cell proliferation was assessed by ki-67 and cell apoptosis was measured on ImageJ software.

Results: Our preliminary data shows that CO(OID) had more ($p \leq 0.05$) articulated mammary branching morphogenesis than CO(CO). OID(CO) displayed marginal increase ($p \leq 0.09$) in the mammary gland area, as well as in the mammary ductal elongation, compared to CO(OID). Additionally, the number of apoptotic cells within mammary ducts and lobules is higher in CO(OID) compared to OID(CO). In contrast, the number of proliferating cells is higher in OID(CO) mammary gland compared to CO(OID).

Conclusion: Altogether, our findings suggest that daughters of overweight fathers have both systemic and mammary gland confined factors alterations that ultimately lead to higher breast cancer risk in adulthood. However, further data is needed to corroborate this hypothesis. Our ongoing mammary tumor transplantation studies should provide further insight.

(Supported by the American Cancer Society.)

#7: Prenatal Exposure to Airborne Polycyclic Aromatic Hydrocarbons and Growth and Development in Adolescent Girls

Kehm RK, Zeinomar N, White M, Herbstman JB, Tehranifar P, Perera F, Miller RL, Terry MB

Purpose of the Study: Polycyclic aromatic hydrocarbons (PAH), by-products of combustion, enter the body from a variety of sources such as gasoline engines, oil burners, and tobacco smoke. PAH are known endocrine disruptors with estrogenic and anti-estrogenic effects. Early exposure to PAH may impact growth and development through biological mechanisms such as estrogen signaling inhibition by aryl hydrocarbon receptor/estrogen receptor crosstalk and changes in estrogen metabolism, thus setting the stage for health outcomes later in life, including breast cancer. In a cohort of girls, ages 11-19 years (median=15.5), we examined the association of prenatal measures of airborne PAH exposure with age at pubertal growth spurt (i.e., changes in growth spurt, underarm hair, pubic hair or skin changes), breast development and menarche, as well as body mass index percentile and percent body fat.

Methods: We studied 201 mother-daughter pairs from the Columbia Center for Children's Environmental Health birth cohort, which recruited non-smoking African American and Dominican American pregnant women in three low-income neighborhoods in New York City (1998-2006). Women wore a small backpack holding a personal ambient air monitor for 2 consecutive days during the 3rd trimester of pregnancy. Concentrations of 8 carcinogenic PAH were summed, natural log-transformed, and categorized into tertiles for analysis. Girls (11-19 years) self-reported growth and pubertal development by questionnaire and were measured for height, weight, and percent body fat by bioimpedance (Omron Handheld HBF-360C). We used multivariable linear regression models adjusted for age, ethnicity, birthweight, gestational age, income, maternal age at menarche and pre-pregnancy obesity.

Summary of Results: Girls with the highest prenatal ambient PAH exposure were on average significantly older at pubertal growth spurt (highest (>2.94 ng/m3) versus lowest (<1.72 ng/m3) tertile: β=0.92 years, 95% CI=0.11-1.73, P=0.03) and menarche (β=0.60 years, 95% CI=0.03-1.17, P=0.04). No differences were found across PAH tertiles for other measures of growth and development.

Conclusion: Prenatal exposure to PAH may delay some aspects of growth and development in adolescent girls, potentially through anti-estrogenic mechanisms.

(Supported by the NIEHS/NCI grant U01 ES026122.)

#8: Pre-conception paternal DDT exposure and programming of metabolic dysfunction and breast cancer risk in offspring

da Cruz RS, Cao H, Cruz MI, Castilho Fontelles C, Nasir A, Benitez C, de Assis S

Background: Breast cancer is the most common cancer in American women, being the second leading cause of cancer-related death in this group. Exposure to environmental chemicals, such as the pesticide DDT (dichlorodiphenyltrichloroethane), has been long suspected to be a contributing factor in the development of metabolic disease and breast cancer. For instance, early life (in utero and early childhood) exposure to DDT has been associated with increased breast cancer risk in women, and these findings are supported by animal studies. While maternal DDT exposure in pregnancy has been linked to metabolic syndrome and breast cancer risk in offspring, the effects of paternal DDT exposure in male germ-line reprogramming and phenotypes in their progeny has not been investigated. Here, we evaluated the effects of pre-conception paternal exposure to DDT on offspring's metabolism and susceptibility of breast cancer, using a mouse model.
Methods: Male mice were exposed to DDT (1.7mg/kg body weight) by oral gavage for two weeks. At the end of this period, DDT and control-vehicle (CO) were housed with female mice, with free access to a standard chow diet, for three days. Pregnancy-onset was assessed by the presence of a vaginal plug. The weight and number of pups per litter were determined two days after birth. Pups were weaned from mothers at 21 days of age, fed a standard chow diet for the extent of the study and weighed weekly. Mammary tumors were induced by subcutaneous administration of 15mg of medroxyprogesterone to six-week-old female offspring, followed by oral administration of 1mg 7, 12- dimethylbenz[a]anthracene once-a-week for 3 weeks.
Results: Paternal DDT exposure reprogramed the sperm small non-coding RNA content. In line with that, DDT offspring had decreased birthweight ($p=0.04$) and weaning weight ($p=0.01$) compared to CO. Further, ancestral DDT exposure caused metabolic dysfunction in offspring ($p<0.05$) at 7 and 22 weeks of age. Further, female offspring of DDT exposed fathers showed alterations in mammary gland development with a non-significant increase in numbers of terminal end buds and lower rates of apoptosis. In line with that, our preliminary data suggest that ancestral paternal exposures to DDT increase breast cancer risk in offspring: Compared to CO, the DDT offspring presented a non-significant increase in mammary tumor incidence and shorter latency to the first-tumor onset. In addition, tumor growth (volume) was significantly increased in DDT offspring compared to CO ($p=0.01$). In conclusion, our findings support a role for DDT exposure from the paternal lineage in metabolic dysfunction and increased breast cancer risk in their offspring.

#9: Genistein prevents activation of mammary tumor immunosuppressive pathways during tamoxifen treatment in rats exposed to obesity-inducing high fat diet in utero

Andrade FO, Zang X, Dani C, Rosim M, Cruz MI, Zwart A, Yu W, Laishram L, HIlakivi-Clarke L

Although tamoxifen (TAM) therapy significantly reduces breast cancer mortality, up to 52% of locally advanced breast cancer (BC) patients recur within 20 years of initial diagnosis. Thus, identification of factors that cause recurrence to prevent it is needed. Maternal obesity may increase BC risk in daughters and our previous preclinical study showed that it increases local mammary tumor recurrence after TAM therapy is completed by 300 percent in the offspring. The increased risk of recurrence was linked to suppression of CD8+ T cytotoxic cells in recurring tumors and upregulation of immunosuppressive pathways. Observational epidemiological studies and our preclinical study indicate that long term consumption of genistein (GEN) in soyfoods reduces the risk of breast cancer recurrence, although GEN is an estrogenic compound and in vitro and in vivo promotes the growth of estrogen receptor positive (ER+) MCF-7 human breast cancer cells. We analyzed here if dietary intake of either 500 ppm GEN, or soy flour (SF) containing 500 ppm GEN, modifies tumor response to TAM in offspring of rat dams fed with control (CO) or obesity-inducing high fat (HF) diet during pregnancy.

Female offspring of Sprague Dawley rats from CO and HF groups were exposed to 7, 12-dimethylbenz[a]anthracene to induce ER+ mammary tumors and treated with TAM (337pm), TAM+GEN or TAM+SF when tumor reach a size of 1.3 cm in diameter. In HF offspring GEN and SF increased TAM resistance, and SF reduced complete responses. GEN and SF increased acquired TAM resistance both among CO and HF offspring. We further found that TAM increased expression of Foxp3 regulatory T cell marker and Tgfβ1 in HF offspring compared with CO group, indicating tumor immunosuppression. GEN reversed the increase of both Foxp3 and Tgfβ1, and increased the expression of CD8+ T cells in HF offspring. GEN also decreased the expression of key inflammatory protein RAGE in HF offspring, whilst SF increased RAGE ligand S100A8 in CO offspring. Although GEN did not improve TAM response, it promoted tumor immune response in HF offspring which raises the possibility that GEN might be effective in preventing tumor recurrence after TAM therapy in offspring of obese mothers.

(Supported by the NIEHS/NCI grant U01 ES026127.)

#10: Assessment of estradiol and endocrine disruptors induced transcriptomic responses

Chen R, Vantangoli M, Boekelheide K, Hartung T, Fornace Jr. AJ, Li HH

The central goal of the Human Toxome Project* is to use complementary "omics" approaches to map and annotate pathway(s) of toxicity (PoT) for a defined set of endocrine disruptors. The transcriptomics team at Georgetown University has carried out a series of studies to assess estradiol and endocrine disruptor-induced changes in gene expression, and compared the estrogenic effects of endocrine disruptors with that of estradiol (E2). We performed microarray and Ingenuity Pathway analysis to elucidate estrogen signaling pathways that were activated/regulated by E2 and endocrine disruptors. In this study, we assessed three well-characterized endocrine disruptors, Bisphenol A (BPA), Diethylstilbestrol (DES), and Genistein (GEN). To assess the transcriptomics responses to these endocrine disruptors, a long-oligo one-color microarray platform was used.Each treatment set included 3 replicates of vehicle controls and 3 replicates of treatments at different concentrations and different time points (very high dose, and effective dose for 6h and 24h). Within each treatment set 1 nM of E2 treatment was included as positive control. The global gene expression profiles of BPA, DES and GEN treatments showed that BPA and GEN treatments induced time-dependent gene expression changes in MCF7 cells, while DES treatment did not induce either time-dependent or dose-dependent gene expression changes. Meanwhile, when cells treated with DES at 10pM or 10nM for 24h, about 95% and 91% of DES up-regulated genes were also up regulated by E2, respectively. This observation suggested that DES has a very similar effect on up-regulation of genes as that caused by E2 treatment. To elucidate estrogen signaling pathways that were activated/regulated by E2 and endocrine disruptors, datasets containing genes that were significantly altered by at least 1.7-fold in each treatment were subjected to Ingenuity Pathway Analysis to find potential pathways that were specific for each agent. By comparing enriched canonical pathways in each treatment, we observed the similarity and the difference between E2 and endocrine disruptors. Pathways involved in cell cycle and DNA damage response, such as Role of BRCA1 in DNA damage response, Cell cycle control of chromosomal replication, Cell cycle: G2/M DNA damage checkpoint regulation, were enriched in all treatments. Two pathways, Glioma invasiveness signaling and Breast Cancer Regulation by Stathmin 1 (STMN1), were significantly altered in BPA and GEN treatments but not in E2 and DES treatments. Regulation of STMN1 is cell cycle dependent, and is controlled by protein kinases, such as CAMK (Ca2+/Calmodulin-dependent protein kinases), MAPKs (Mitogen-activated protein kinases), PKA (cAMP dependent protein kinase), in response to cell signals. The upstream factors that activate kinases to modulate STMN1 functions include GPCRs that are activated by hormones and neurotransmitters. The pathway analysis result suggested that BPA and GEN bind to the G-protein coupled receptor, GPR30, of MCF7 cells to regulate protein kinases, which in turn can modulate STMN1 phosphorylation, microtubule stability and ultimately control cell cycle. In conclusion, microarray combined with pathway analysis showed that BPA and GEN can bind to GPR30 and activate GPR30 mediated signaling pathway, while E2 and DES did not activate GPR30 signaling pathway under current experimental conditions.

(Supported by the NIEHS grant R01 ES020750.)

#11: In utero exposure to ethinyl estradiol predisposes to the development of mammary tumors with an aggressive/endocrine resistant phenotype

Bouker KB, de Oliveira Andrade F, Jin L, Hilakivi-Clarke L

It is well known that in utero estrogenic exposures influence later breast cancer risk in offspring. We previously found that in utero exposure to ethinyl estradiol (EE2) caused a multigenerational increase in rat mammary cancer risk and increased resistance to the antiestrogen tamoxifen (TAM). Our current study uses our preclinical model that recapitulates the clinical picture of TAM resistance and tests whether the combination of TAM with drugs that alter the epigenome can prevent TAM resistance. Rats exposed to EE2 in utero showed significantly more de novo (R) and acquired (AR) resistance compared to controls. The concurrent use of the histone deacetylase inhibitor valproic acid (VPA) and DNA methyltransferase inhibitor hydralazine (H) with TAM as a 1st line therapy markedly altered the response profile of the in utero EE2 exposed rats reducing R by 33% and reducing AR by 75%. Importantly, the addition of VPA/H in control animals led to significantly worse outcomes including >2 times higher incidence of the AR. iTraq-based proteomics analysis comparing pre-TAM treatment biopsies from in utero EE2 and controls identified 188 differentially expressed proteins. 6 proteins correlated with both in utero EE2 exposure and TAM resistance. Most interesting among these is CD44, a breast cancer stem cell marker that associated with breast cancer aggressiveness in vivo and TAM resistance in vitro. CD44 expression is increased by 2.4-fold in biopsies from in utero EE2 exposed/TAM resistant biopsies. Our data suggest that tumors arising in in utero EE2 exposed animals have more stem-like features and a more aggressive/resistant phenotype. Analysis of tumors taken at the end of the treatment showed the differential expression of genes related to epithelial to mesenchymal transition, immunosuppression and epigenetic regulation between in utero EE2 and control animals. Given the prevalence of estrogenic chemicals in our food and water supply it is likely that the number of women exposed to increased levels of estrogenic chemicals in the womb is high. If these women have an increase in TAM resistant breast cancer, as our data suggest, it is critical to find effective treatment regimens, as women with recurrent tumors are the most likely to die of their disease.

(Supported by the DOD W81XWH-14-1-0031, NCI grant U54 CA149147, and NCI grant R01 CA164384.)

#12: Association of PBDEs and BPA and epigenome modulation in sera of women at the menopausal transition

Ding YC, Steele L, Kanaya N, Rakoff M, Reynolds P, Nelson D, Chen S, Neuhausen SL

Growing evidence from epidemiology and experimental model studies suggests that endocrine- disrupting Chemicals (EDCs) in the environment may modify the risk of developing breast cancer. We hypothesize that during the menopausal transition, polybrominated diphenyl ethers (PBDEs) and bis-phenol A(BPA) will promote the development of hormone-responsive breast cancers.
Methods: We tested the associations of these chemicals on the epigenome in 316 healthy women between ages 40 to 58 years at time of blood draw participating in the prospective California Teacher's Study (CTS). We measured gene-specific methylation using the Illumina EPIC Methylation chip, global methylation using pyrosequencing for Alu and LINE-1 elements, and miRNAs using miRNAseq.
Results: We identified 157 differentially methylated regions (DMRs) associated with the exposure of three BDE congeners and BPA (mFDR < 0.05). Top pathways enriched among genes in those DMRs linked to cellular metabolism and Aryl Hydrocarbon Receptor Signaling pathway. Based on the magnitude of association, the top 34 DMRs were selected for validation using targeted bisulfite sequencing. Interestingly, in 28 of the 34 top DMRs, decreased methylation was observed, indicating that the PBDE congeners and BPA more often are enhancing gene expression. This result is concordant with our in-vitro analysis of PBDE-treated cell lines where there were more hypomethylation than hypermethylation events. For global methylation, there were associations of Alu but not Line-1 elements, with positive associations with BDE100 and BDE153. A total of 66 differentially expressed miRNAs (DEmiRs) were identified with FDR >< 0.25 for the PBDEs and BPA.

We have validated the results for 21 DMRs and are now testing whether these biomarkers of exposure are associated with breast cancer in 246 breast cancer cases diagnosed between ages 40 and 58 years in the CTS nested case-control study. Similarly, we will conduct pyrosequencing for the cases to assess the association of Alu methylation and breast cancer. Individual and combined effects of the PBDEs and BPA on the development of breast cancer will be presented. This study assess the potential effects of EDC exposure on epigenetic modulation that may confer risk of developing breast cancer.

(Supported by the NIEHS/NCI grant U01 ES026137, and the NCI/NIH grant P30 CA033572.)

Communication Science

#13: Comparing Caregivers' Perceived Risk of Breast and Skin Cancer for Children: Implications for Breast Cancer and Environment Risk Communication

Silk, KJ and Totzkay, D

Recent biomedical research has focused on the study of environmental exposures and lifestyle factors that influence breast cancer development. One emerging risk factor is Benzophenone-3, commonly referred to as oxybenzone, a chemical ultraviolet ray blocker found in common sunscreens (Coronado et al, 2008; Mohanmmad & Berry, 2014; Nakagawa & Suzuki, 2002). Preliminary evidence in rodent mammary gland models, which mirror human mammary gland development (Russo, 2015), has found that exposure to oxybenzone increases the likelihood of cancerous cells developing. In response to this emerging science on ozybenzone and breast cancer risk, formative research on relevant risk perceptions is needed in order to better communicate about and motivate risk reduction behaviors.

One risk perception relevant to oxybenzone relates to the contrast that exists between the risk of breast cancer and skin cancer. While oxybenzone in sunscreen is a potential breast cancer risk, sunscreen is a widely-accepted risk reduction behavior for skin cancer. Early qualitative evidence suggests people are hesitant to prioritize breast cancer risk reduction over skin cancer risk reduction in this context. This could be due to the fact that skin cancer risks are seen as more modifiable, while breast cancer risks are seen as more based on genetics or family history. Before messaging can be done to motivate risk reduction through the avoidance of oxybenzone in sunscreens, formative research is necessary to understand how risk perceptions of breast cancer compare to risk perceptions of skin cancer. This research is important because breast cancer and skin cancer risk perceptions will impact individuals' receptiveness to messages that may ask them to reduce exposure to oxybenzone.

In order to assess these risk perceptions, two studies are presented. The first includes a survey disseminated at a local health fair with a total of 34 Likert-type items regarding: 1) parents' perceived severity of breast/skin cancer; 2) their perception of their child's susceptibility to developing breast/skin cancer; 3) their perceived self-efficacy in preventing breast/skin cancer in their child; 4) their perception of response efficacy regarding breast/skin cancer prevention strategies; 5) and their beliefs on genetic determinism, or the degree to which genetics versus lifestyle determine the risk of breast/skin cancer. Demographic data were also collected. Preliminary analyses of these data show the sample tended to be ambivalent about their children being at risk of developing breast cancer in their lifetime, but perceived a higher risk of their children being at risk to develop skin cancer. Differences in self-efficacy beliefs also appeared, with respondents reporting low self-efficacy beliefs for breast cancer prevention and relatively high self-efficacy beliefs for skin cancer prevention. Additionally, there is apparent agreement with breast cancer genetic determinism beliefs, and disagreement with skin cancer genetic determinism beliefs. A follow up study is then presented that collects comparative risk perceptions between breast and skin cancers, as well motivation and willingness to enact several risk reduction behaviors. Specifically, caregivers are asked to make risk perception estimates for both skin cancer and breast cancer, this time regarding their own risk, as well as their willingness to partake in a number of sun protection behaviors in different contexts. They will also make comparative risk estimates, such that they will rate the extent they think breast cancer or skin cancer is more severe and likely to affect them, as well as whether they are more confident in their ability to reduce risk for one over the other and if recommendations for risk reduction are more effective for one over the other.

Data collection for this second study is presently underway and findings will be presented alongside the aforementioned findings. This presentation will discuss implications of these results for the development of breast cancer risk reduction messages geared toward parents and caregivers that discussion the potential risk associated with oxybenzone.

Community Outreach and Dissemination

#14: Lay perceptions of breast density and breast cancer risk

Totzkay D, Thomas B, Silk KJ, Thompson A, Quaderer T, Miller K, Gabrell M, Newkirk C, Carter E, Brody J, Ohayon J, Burke K, Symington A

Breast density has received an increased amount of attention in women's health research due to its possible link to breast cancer. Breast density may not only be linked to cancer directly, but also makes it difficult to see cancerous materials in mammographic screenings due to the material make-up on dense breasts. Although research continues to delve deeper into the potential connection between dense breasts and breast cancer, there still remains a great deal of uncertainty regarding dense breasts, especially among lay women. This study presents an analysis of information obtained from 16 focus groups consisting of 140 women across 5 different locations. Results indicate that understanding of breast density is indeed limited. Results also show participants are unsure of the causes and implications of breast density, as well as of health care providers' knowledge. There is additional evidence of misunderstandings around the concept of breast density that may be from confusion on the part of health care provider or some other source. This study provides a foundation for further investigation of issues surrounding breast density and other future directions. Implications for breast density notifications and policy relating to breast density are also discussed.

(Supported by the NIEHS/NCI grant U01 ES026127.)

#15: Empowering youth in cancer risk reduction through education: preliminary findings

Zeinomar N, Burke KR, Grant-Alfieri A, de Hoz M, Herbstman JB, Miller RL, Perera FP, Terry MB

Purpose: There is mounting evidence that cancer prevention, including interventions against lifestyle and environmental risk factors, should occur early and during vulnerable time windows of susceptibility, for maximal impact. As such, we collaborated with WE ACT for Environmental Justice (WE ACT) to develop a cancer prevention high school curriculum.
Methods: We developed a 50-minute module on cancer prevention to be administered as part of WE ACT's Environmental Health and Justice Leadership Training (EHJLT) at Washington Heights Expeditionary Learning School (WHEELS) located in Northern Manhattan. The module included an introduction to cancer biology, cancer burden in their local communities, risk reduction strategies, and pedigrees and gene-environment interactions. We also embedded an interactive activity within the module that required students to identify risk factors and brainstorm strategies for risk reduction at two different levels, individual and community. We assessed knowledge through an aggregate pre- (directly before class) and post- (up to one week after) survey that was administered through Kahoot, a game based quizzing platform. We also administered this module to high school students in Columbia University's Cancer Center CURE summer program.
Results: We successfully administered the cancer prevention module to 2 classrooms of 23 students total at WHEELS and to 30 CURE students. We found that there was overall improvement in knowledge post-education. The question about cancer burden: "How many people in the U.S. are diagnosed with cancer every year?" had the lowest baseline knowledge (28% answered correctly) in both groups and the greatest improvement post-education (59% improvement post education). Similarly, we observed low levels of knowledge pre-education on basic cancer biology, carcinogens, and risk factors. For example, on the pre-survey, 51% of students correctly answered "What is a carcinogen?", but we observed a 26% improvement in knowledge post-education.

Conclusions: We developed an interactive cancer prevention module that can be adopted by other BCERP sites to improve knowledge on risk reduction, cancer prevention, and possibly empower youth to take action in reducing their cancer risk and their communities'.

(Supported by the NIEHS/NCI grant U01 ES026122.)

#16: Exploring glyphosate-based herbicide effects on liver gene expression in rats and assessing knowledge of pesticides in Long Island communities

Frawley S*, Roberts S*, Deyssenroth MA, Lesseur C, Ma Y, Chen J, Evans S

Pesticides are used to control unwanted organisms. Herbicides, a form of pesticides, target unwanted plants such as weeds. The most widely used herbicide in the United States is glyphosate, the active ingredient in RoundUp and other commercial products. Although human glyphosate-based herbicide (GBH) exposures are widespread, few research studies focus on possible GBH health effects in children, and the general public is largely uninformed about potential risks of exposure. Evidence from animal studies suggests that GBHs accumulate in the liver. The aims of this study were 1) to investigate possible effects of GBHs on liver gene expression in developing rodents and 2) to assess our community's knowledge on pesticide use and risks in order to inform the creation of an educational campaign. Female Sprague-Dawley rats were exposed to 1.75 mg/kg bw/day glyphosate or RoundUp through drinking water from gestational day 6 (through their dams) to postnatal day 140. Liver RNA was extracted and reversed transcribed. We quantified Srebf1 and Acaca gene expression using qPCR. Srebf1 expression was marginally upregulated in glyphosate-exposed rats ($p=0.07$) and Roundup-exposed rats ($p=0.08$) compared to control. Acaca expression was marginally upregulated in glyphosate-exposed ($p=0.03$) and Roundup-exposed ($p=0.15$) rats. These gene expression changes suggest altered cholesterol regulation pathways. To assess pesticide usage and risk perception in our community, we administered a ten question anonymous survey through social media. 82 participants responded (73.5% female, 26.5% male), with a mean age of 30 (+/- 19). Over 60% expressed strong concerns over pesticide exposure. 44.4% of participants reported using pesticides. However, only 38.5% knew what type of pesticides (synthetic or organic) were applied by landscapers on their property. These findings suggest that individuals are largely unaware of their own pesticide exposures and the associated potential risks. Thus, we will create an educational video and information sheets regarding pesticide usage and risks. In addition, this campaign will encourage community members to support legislation that will protect them from harmful pesticide exposures. This information will be shared online, in schools, and in science fairs.

*Indicates a recipient of an honorarium

#17: To Replace Toxins Linked with Breast Cancer: Applications of Sophorolipid Butyl Ester in the Stabilization of O/W Emulsions for a Novel Food Packaging Material

Lin R, Abizadeh E

Purpose: The purpose of this study is to investigate the optimal component substances and concentrations for the stabilization of oil-in-water emulsions using sophorolipid-butyl ester (SL-BE) as a nontoxic emulsifier with some antimicrobial capabilities. The use of essential oils in the O/W emulsions along with poly-γ-glutamic acid (γPGA) can be applied to create films with antimicrobial and antioxidant properties. These films are capable of replacing common preservatives, such as sulfites, formaldehydes, sorbates, nitrates, and benzoates, which have been associated with adverse health effects. These films could reduce the need for food packaging and wrappers produced using BPA and PFOA, toxic chemicals linked to breast cancer.
Methods: Emulsions of differing compositions and formulation procedures were tested for macroscopic and microscopic droplet stability. Lemon oil and oregano oil were tested. Component concentrations, time after homogenization before analyses, incubation temperatures, and homogenization durations were varied during testing. Pictures were taken using smartphone cameras and optical microscopes, and z-average droplet diameters were analyzed using a dynamic light scattering (DLS) machine.
Summary: Oregano oil emulsions generally remained more stable than lemon oil emulsions. SL-BE effectively stabilized emulsions, improving with greater concentrations relative to oil concentration.

γPGA offered additional emulsion stability at greater masses. Formulation procedures also influenced emulsion stability.
Conclusions: The data indicates that SL-BE and γPGA can be utilized to stabilize essential oil-in-water emulsions. γPGA, a hydrophilic polymer, can produce solutions that, when dried, will form antimicrobial and antioxidant films. These films may be utilized for food packaging, preventing microbial and oxidative spoilage and replacing common preservatives and packaging materials linked with breast cancer. Future research should be applied to pH-controlled emulsions and optimal emulsion formulations.

(Supported by the Great Neck Breast Cancer Coalition.)

#18: Engaging community members to accelerate translational research on breast cancer and the environment

Serrano M, Rakoff M, CLC, Neuhausen S, Chen S, Ashing KT, Bernstein L

Introduction: Engaging diverse community members in research is vital to communicate and disseminate information to their communities. Despite the availability of print and web-based informational resources on breast cancer and the environment, surprisingly few resources are readily available, evidence-based, and understandable and usable by the advocacy community and general public.
Purpose: To create a Community Leadership Committee (CLC) that represents the demographics of the Greater Los Angeles area to aid in dissemination of research findings from the BCERP.
Methods: Members of the CLC were drawn from community and advocacy organizations, representing the four largest ethnic/racial groups (White, Black, Chinese, Latina). Three representatives and their alternates from each group meet three times a year. The primary role of the CLC is to help create teachable, culturally-responsive materials on breast cancer and the environment to educate diverse communities. They help tailor and disseminate information in the most appropriate and understandable manner to different groups and act as liaisons, thus creating a bi-directional learning environment. Focus groups were used to evaluate messaging and materials.
Results: The CLC developed educational materials for broad community dissemination, including a breast-cancer risk-factors infographic and a magnet describing reliable sources of information, both in three languages (English, Spanish, Chinese), and a website dedicated to breast cancer and the environment. Focus groups were held to evaluate the educational materials for content and cultural appropriateness and effectiveness. In total, 6 focus groups were conducted with 4 groups in English [Black, White, Chinese, and Latina, 1 group in Spanish, and 1 group in Chinese. Their evaluations were used to further hone the materials in the CLC.
Conclusion: The dissemination of educational materials to multi-culturally diverse communities through workshops, forums, social media and via our website will create public benefit. We expect this work to result in better understanding of environmental risks in the community leading to better community uptake of strategies to reduce or mitigate exposures and for community involvement to effect policy changes.

(Supported by the NIEHS/NCI grant U01 ES026137.)

Breast Density

#19: Relationship of epithelial nuclear density with measures of terminal ductal lobular unit involution and mammographic density

*Mullooly M, *Puvanesarajah S, Fan S, Pfeiffer RM, Olsson L, Hada M, Kirk EL, Vacek PM, Weaver DL, Shepherd JA, Mahmoudzadeh AP, Wang J, Hewitt SM, Herschorn SD, &Sherman ME, &Troester MA, &Gierach GL (Equal contribution as *first authors and & senior authors)

Purpose: Elevated mammographic density (MD) and reduced terminal ductal lobular unit (TDLU) involution are correlated yet independently associated with increased breast cancer risk. A previous digital histologic study found significant positive associations between automated quantitatively assessed epithelial nuclear density (END) and visual TDLU measurements in normal breast tissue. In this study, we assessed relationships between END with TDLUs and MD among women diagnosed with benign breast disease (BBD).

Methods: TDLU density (count/mm2) was visually assessed on normal background tissue from 262 digitized imaged-guided biopsy targets (n=224 patients). END was automatically analyzed using Aperio's Genie Classifier. Global and local MD were determined using single X-ray Absorptiometry of pre-biopsy craniocaudal digital mammograms. Ordinal multivariate logistic regression examined associations between tertiles of TDLU density and END. Analyses of covariance examined mean MD across tertiles of END.
Results: Overall, END was positively associated with the highest tertile of TDLU density, adjusted for age and BMI: Odds Ratio (OR): 3.42, 95% Confidence Interval (CI): 1.87, 6.28. Similar associations were observed among patients diagnosed with non-proliferative (OR: 3.11, 95%CI: 1.15, 8.42) and proliferative BBD (OR: 3.07, 95%CI: 1.46, 6.45). In analyses stratified by menopausal status, the positive relation between END and TDLU density was observed in premenopausal (p-trend<0.001), but not postmenopausal (p-trend=0.67) women. No associations were observed between END and global MD; however, END was positively associated with localized peri-lesional MD (p-trend=0.02). This association attenuated when analyses were stratified by BBD subtype.
Conclusions: Among women undergoing diagnostic breast biopsy, we observed significant positive associations between automated END and visually assessed TDLUs in benign biopsies. However, strengths of associations varied by menopausal status. Further, unlike prior studies of TDLUs and MD, no associations were observed between END and global MD. Positive associations observed between END and local MD measures highlight the importance of investigating the role of the microenvironment in the progression of breast precursor lesion.

(Supported by the NCI Intramural Research Program.)

Mechanisms of Breast Cancer Development

#20: Progesterone Receptor Activation by Metallohormones

Yan G, Divekar SD, Gahtani R, Shi X, Shiroma J, Alolaqi F, Alagl S, Shinn J, Dakshanamurthy S, Martin MB

A major risk factor for breast cancer is exposure to estrogen during reproductive and post-menopausal years. However, findings from the Women's Health Initiative showed that hormone therapy with estrogen plus progestin was associated with higher incidence of breast cancer, implicating progesterone as another oncogenic driver. A group of metals and metalloids, including bivalent cations and oxyanions, can act as metalloestrogens to directly activate estrogen receptor alpha (ERa) to induce mammary gland growth and differentiation. Furthermore, higher tumor incidence and earlier tumor onset were observed when virgin female rats were fed an environmentally relevant dose of cadmium or arsenite through diet and challenged with dimethylbenzanthracene. Preliminary in vitro data suggest that bivalent metal cations can also activate progesterone receptor B (PRB). Following metal treatment, PRB target genes were induced in T47D-Co cells, which constitutively express PR, as well as in HEK293T cells transiently expressing PRB. Based on structural similarities of the ligand binding domains (LBDs) among steroid hormone receptors and previously identified interaction sites for calcium and cadmium in the LBD of ER, putative metal binding residues in PRB are evaluated by transient expression of amino acid-substituted PRB mutants in HEK293T cells. We seek to delineate the biochemical mechanism of PRB activation by the metals as well as the subsequent biological effects on mammary gland development and carcinogenesis.

(Supported by the NIEHS/NCI grant U01 ES026132.)

#21: Prioritizing Breast Cancer Susceptibility from Early-Life Chemical Exposures in Toxicity Testing

Hindman AR, Rudel RA

Current toxicological methods must keep pace with chemical development and confront the challenges that exposure to hormone-like environmental chemicals, known as endocrine disrupting chemicals (EDCs) pose to human health. EDC exposure is particularly detrimental during key developmental windows, such as in utero and early-life. Traditional whole animal toxicity studies do not assess mechanisms of latent biological effects following early-life exposures. Further, the traditional focus on apical, late-stage endpoints is not sensitive to developmental disruptions that promote disease susceptibilities. Evidence from the synthetic estrogen diethylstilbestrol (DES) links early-life EDC exposure and increased later-life breast cancer (BC) risk.

Promoting thorough mechanistic understanding can prioritize other EDCs for chemical screening that demonstrate similar effects and BC risk as DES. We are reviewing and organizing existing mechanistic data linking low-dose, early-life EDC exposure and BC susceptibility using the Adverse Outcome Pathway (AOP) framework. AOPs leverage existing knowledge to connect a molecular initiating event (MIE) by a chemical stressor to an adverse outcome (AO). Identification of the most critical intermediate and measurable biological key events (KEs) facilitates this link and supports the shifting toxicity-testing paradigm towards efficient, high-throughput and in vitro methods. Based on extensive evidence from studies of early-life DES and bisphenol A (BPA) exposures in rodents, estrogen receptor activation serves as the MIE for our developing AOP. AOs preceding toxicity and cancer include altered mammary gland (MG) epigenetics, morphology, density and hormone sensitivity, leading to enhanced BC susceptibility. By integrating data about these chemical perturbations with known normal MG biology, we can identify data gaps and solicit new evidence. Similar to the way monitoring mammographic breast density asserts BC risk and prevention, our application of the AOP framework aims to establish AOs of susceptibility as relevant and more sensitive hazard endpoints in chemical testing. This AOP will facilitate assay development to predict BC risk and provide a means to begin categorizing classes of EDCs based on their relationship to AOs.

(Supported by the NIEHS/NCI grant T32 ES023769.)

#22: Prenatal and pregnancy PAH alter DNA methylation in breast cancer genes belonging to AHR/ARNT/AHRR pathway

Sahay D*, Jezioro JR, Rivera JA, Yan B, Szabolcs M, Terry MB, and Miller RL

Polycyclic aromatic hydrocarbons (PAH) are ubiquitous environmental pollutants generated from incomplete combustion. They possess carcinogenic and endocrine-disrupting properties. Despite accumulating epidemiological data supporting the association between PAH exposure and breast cancer risk, few experiments have tested the prenatal and pregnancy time windows of exposure on subsequent BC risk. We hypothesize pregnancy/prenatal PAH exposure will alter DNA methylation/gene expression in BC candidate genes belonging to the AHR/AHRR/ERα pathway and induce histological atypia in the mammary glands of mice offspring and grand-offspring.

Pregnant dams were exposed to a nebulized mixture of 9 PAH vs negative control aerosol 5 days a week, for 3 weeks. RNA and DNA were extracted from the mammary glands - the delivered dams at postpartum day (PPD) 28 and F1 offspring and F2 grandoffspring at postnatal days (PND) 28 and 60. Reverse transcriptase-real time PCR and pyrosequencing was performed for AHRR, ARNT (Aryl hydrocarbon receptor repressor pathway), ERα (Estrogen signaling pathway), PPARγ (Lipid metabolism pathway), and BRCA1 (DNA repair pathway) gene expression and DNA methylation analyses respectively. Hematoxylin and Eosin staining was performed on the mammary glands and assessed for histological hyperplasia, atypia and inflammation.

Pregnancy and prenatal PAH exposure decreased AHRR mRNA expression ($p<0.05$) with a trend of hypermethylation of CpG-329 ($p=0.10$). Pregnancy and prenatal PAH exposure decreased ERα mRNA expression and hypermethylated several CpG sites at the ERα promoter region ($p<0.05$ for each). An increased PPARγ mRNA expression with hypomethylation in the PPARγ promoter region was observed in the PAH exposed mammary tissues ($p<0.05$ for each). PAH exposure decreased mRNA levels of BRCA1 in the F1 offspring ($p<0.05$). We observed similar associations with prenatal PAH exposure in mammary tissue of F2 grandoffspring. Further, prenatal PAH induced more frequent cellular hyperplasia in a subset at PND 60 (F1: Control 2/9 vs. PAH 6/9 mice; F2: Control 1/8 vs. PAH 4/7 mice).

Preliminary results suggest prenatal PAH exposure may hypermethylate AHRR and ERα, hypomethylate PPARγ, decrease mRNA expression of BRCA1, and induce more frequent breast cellular hyperplasia

(Supported by the NIEHS/NCI grant U01 ES026122.)

*Indicates a recipient of a travel scholarship

#23: Benzophenone-3 (BP3) exposure increases TGFβ expression in mouse and human mammary tissues

Gregory KJ, Morin S, Jerry DJ, Vandenberg L, Schneider SS

The TGF beta family of ligands are multifunctional cytokines that are critical for controlling morphogenesis, stem cell differentiation, inflammation and cellular homeostasis. There are 3 prototypic TGFb ligands (TGFb1,2,3) that have partially overlapping expression patterns in the human breast. TGFb1 is the most widely expressed ligand. It is present in both the terminal end buds as well as the mammary stroma. Transcription of TGFb 2 and 3 undergo striking increases with pregnancy. This study was performed to determine whether exposure to BP3 during pregnancy, could affect the expression of these critical family members.

6 week old BALB/c mice were impregnated and treated with BP3 during pregnancy and lactation (6 weeks) at 3 doses tolerable daily intake (TDI) 30ug/kg/day, (95P) 212 mg/kg/day and the no observed adverse effect (NOA) 3000ug/kg/day. qRT-PCR was performed on mammary glands to examine TGFb family member and target gene expression changes. Gene expression changes were also examined in human explant cultures and primary human epithelial cell lines treated directly or with conditioned media from BP3 treated macrophages.

We found persistent and significant increases in both TGFb1 and TGFb3, but not TGFb2 in the mammary glands of mice exposed to the highest level of BP3. Downstream targets of TGFb1 (ColA1, OPN and VCAN) were examined to see if there is a suggestion of increased TGFβ activity. We observed significant increase in OPN at the NOA dose and an increases in ColA1 which is close to significant p=.078, but no change in VCAN. TGFb3 was seen to increase in human explant cultures by 30 mM BP3 however TGFb1 displayed variable effects. While direct treatment of HMECs did not affect TGFb1 expression, conditioned media from BP3 treated macrophages increased TGFb1 in the primary mammary epithelial cells.BP3 treatment significantly increases TGFb1&3 expression in mammary tissue and it is consistent with increases in two TGFb target genes, OPN and ColA1. It suggests a mechanism for alterations proliferation, apoptosis and immunosurveillance.

(Supported by the NIEHS/NCI grant U01 ES026127.)

#24: Elucidating the effects of Polybrominated Diphenyl Ether (PBDE) on mouse mammary glands through single-cell RNA sequencing analysis

Kanaya N, Chang G*, Wu X, Bernal L, Wang J, Warden C, Yamamoto T, Li J, Park JS, Synold TW, Neuhausen SL, Chen S

Polybrominated Diphenyl Ethers (PBDEs) have been used as flame retardants in household materials. Their environmental persistence has led to continuous human exposure at significant concentrations in tissues. PBDEs are thought to be endocrine disrupting chemicals and are associated with a variety adverse health effects. Yet, the relationship between breast cancer risk and the biological activity of PBDEs in the mammary glands is poorly understood. Since BDE-47, BDE-100 and BDE-153 are three major PBDE congeners in human serum, we examined the in vivo effects of these PBDEs using ovariectomized mice, a surgical menopause model. In the presence of physiologically-relevant dosage of 17β-estradiol (E2), PBDE-treated mouse mammary glands exhibited a large number of terminal end bud-like structures with multicellular layered structures and Ki67-positive cells. RNA-sequencing results suggest that PBDEs augment the estrogen-mediated cell proliferation and modulate immune regulation in mammary glands. In order to elucidate the effects of PBDEs on different cell types, single-cell RNA sequencing (scRNA-seq) analysis has been performed. We digested the mammary glands from control (vehicle), E2, or E2+PBDE treated mice into single cells. All samples were prepared for scRNA-seq using 10x Genomics platform. Our results revealed that PBDE increased the number of ER+/PR+ and ER-/PR+ cells in two luminal epithelial populations (hormone-responsive/mature luminal and secretory/luminal progenitor). Furthermore, E2 and PBDE treatments increased c-Kit+ cells. Moreover, the M2 macrophage population was increased, suggesting cross talk between immune cells andepithelial cells. Our results can potentially advance our understanding of, at the single cell level, how PBDE exposure during menopausal transition can modify mammary gland structure and increase the risk of developing breast cancer.

(Supported by the NIEHS/NCI grant U01 ES026137.)

*Indicates a recipient of a travel scholarship

Windows of Susceptibility

#25: The effects of pubertal exposure to benzyl butyl phthalate (BBP), perfluorooctanoic acid (PFOA), and zeranol on the uterus and the serum levels of estrogen and progesterone in the female Sprague-Dawley rats

Gurdogan H, Kanefsky J, Santucci-Pereira J, Su Y, Russo J

Chemicals commonly found in the environment that can interfere with the body's endocrine system are a matter of major concern and debate. Animal studies, as well as data from epidemiological observations, have shown a link between some endocrine disrupting chemicals (EDCs) and reproductive tract dysfunction, hormonal imbalances and susceptibility to cancer. Growing scientific evidence correlating exposure to environmental toxicants with disturbances in critical biological systems has raised awareness about the problem, but the effects of EDCs during important windows of development such as the pubertal period remains unclear. In this study, we proposed to evaluate the short and long term effects of three widespread EDCs on the serum levels of ovarian hormones and the uterus morphology of female Sprague-Dawley rats. Animals were exposed to benzyl butyl phthalate (BBP), perfluorooctanoic acid (PFOA) and zeranol, either singularly or in combination, at the pubertal period (21 to 42 days of age). As most endocrine disruptors show different effects for different doses, two experimental doses were tested. At 50 and 100 days of age, we collected blood samples to measure estradiol (E2) and progesterone (P) concentrations, and the uterus to conduct morphological analyses. Some uterotrophic assays in rodents have shown that EDCs may induce estrogenic changes as demonstrated by an increased height of luminal epithelial cells and increased weight. However, we found no significant changes in the uterine luminal epithelial height, suggesting that the regimen doses chosen for this study do not affect uterine lining when compared to a control group. Likewise, the levels of ovary-derived hormones were not altered at 50 or 100 days of age.

Our results show that estradiol and progesterone concentrations were influenced by estrous phase, indicating that the doses of chemical exposure used in this study, which reflect the level of exposure in humans, did not disrupt ovarian normal functioning in regards to E2 and P production.

(Supported by the NIEHS/NCI grant U01 ES026130 and NCI/NHI Cancer Support Grant P30 CA006927.)

#26: Pubertal exposure to perfluorooctanoic acid (PFOA), butyl-benzyl phthalate (BBP), and zeranol do not affect the expression of estrogen receptor in the Sprague-Dawley rat's mammary gland.

Bondy JI, Cormier NB, Khouri PS, Zafar A, Good P, Santucci-Pereira J, Su Y, Kanefsky J, and Russo J

Breast cancer is a hormone dependent disease with increasing occurrence in women. Despite the unknown etiology for this rise, epidemiological data indicates a possible association between carcinogenesis and endocrine disrupting chemicals (EDCs). Organisms are ubiquitously exposed to EDCs, which are compounds that alter cellular behavior by interfering with various hormone pathways. A primary hormone that could be affected is estrogen, which binds to estrogen receptors (ER) and plays a role in the maturation of the mammary gland. In this experiment, we investigated the effects of perfluorooctanoic acid (PFOA), butyl-benzyl phthalate (BBP), and zeranol (Zer) exposure during a crucial developmental period, puberty, on the expression of ER in the rat mammary gland. Female Sprague-Dawley rats were separated into a control and ten experimental groups (10-12 animals per group). Animals were exposed by gavage to either PFOA (0.01 or 0.1 mg/kg), Zer (0.01 or 0.1 mg/kg), BBP (0.5 or 5mg/kg), or to the combinations of these EDCs at the corresponding lower doses, from day 21 to 42 of age. The rats were sacrificed and had their mammary glands collected at 50 or 100 days of age to evaluate the short and long term effects of these EDCs. Immunohistochemistry was performed in paraffin embedded sections of mammary gland using an antibody against ER alpha protein (Santa Cruz, Cat# SC-542, Dilution 1:400). Sections were imaged and approximately 50,000 cells were counted per animal to determine the percentage of ER positive cells. ANOVA tests were performed at each age separately.

Our results show no significant difference in percentage of ER positive cells in rat mammary gland at the age of 50 days (p-value=0.74) or 100 days (p value=0.21). Pubertal exposure to BBP, PFOA, and Zer at doses that mimic environmental exposure does not induce short or long term changes in ER expression in the mammary gland of Sprague-Dawley rats. However, it is uncertain whether higher doses or exposure to these EDCs at different developmental periods would affect ER expression. Despite a lack of change in ER expression, EDCs might alter endocrine function through other pathways independent of ER level.

(Supported by the NIEHS/NCI grant U01 ES026130 and NCI/NHI Cancer Support Grant P30 CA006927.)

#27: Pubertal exposure to PFOA and zeranol induces gene expression changes in the mammary gland of Sprague-Dawley rats

Santucci-Pereira J, Kanefsky J, Su Y, Russo J.

Xenobiotics such as perfluorooctanoic acid (PFOA), butyl benzyl phthalate (BBP), and zeranol (Zer) are endocrine disrupting chemicals (EDCs) that may affect mammary gland susceptibility to carcinogenesis. In this work, we evaluated the effect of pubertal exposure to these EDCs on gene expression of the rat mammary gland. Female Sprague-Dawley rats were exposed during puberty (21 to 42 days of age) to environmental-mimicking doses of BBP, PFOA or Zer, individually or in combination. Mammary glands were collected at 50 days of age, RNA was isolated and RNA sequencing was performed. Differentially expressed genes were identified using two different methodologies, DESeq2 and LIMMA (voom with sample quality weights). While there were no accentuated morphological alterations in the mammary gland of exposed animals compared to the control, we found striking changes in gene expression. Using DESeq2, which tests for differential expression based on a negative binomial distribution model, we identified genes differentially expressed (false discovery rate (FDR)<0.10) by Zer (172 up and 3 down-regulated), BBP+PFOA (26 up and 2 down) and PFOA+Zer (264 up and 41 down). The other groups showed few (><4) or no gene being differentially expressed. With LIMMA, which uses empirical Bayes moderated t-statistics, we found changes (FDR><5 and at least two fold change) induced by BBP+Zer (22 up and 12 down-regulated), PFOA+Zer (342 up and 1004 down) and BBP+PFOA+Zer (7 up and 4 down). PFOA+Zer group had the largest number of differentially expressed genes identified by both methodologies. Gene ontology enrichment analyses demonstrated that genes up-regulated by PFOA+Zer were related to metabolic processes, while the down-regulated genes were related to
morphogenesis, differentiation and development. Although the different methodologies present divergent results, both indicate that pubertal exposure to low doses of PFOA+Zer induces changes on gene expression in the mammary gland. Based on this data and on the biological processes potentially affected by these genes, we predict that the pubertal exposure to PFOA+Zer increases the susceptibility of the mammary gland to carcinogenesis.

(Supported by the NIEHS/NCI grant U01 ES026130 and NCI/NHI Cancer Support Grant P30 CA006927.)

#28: Impact of pubertal exposure to BBP, PFOA, or zeranol, alone or in combination, on the proliferative activity of the mammary gland of Sprague-Dawley rats

Erlich M, Scotto F, Torres O, Werts M, Santucci-Pereira J, Su Y, Kanefsky J, Russo J

Butyl benzyl phthalate (BBP), perfluorooctanoic acid (PFOA), and zeranol (Zer), prevalent in the environment, are known endocrine disrupting chemicals (EDCs) causing adverse health effects. These chemicals are likely to have a greater biological effect when exposure occurs during critical windows of development. We evaluated cell proliferation as one of the markers of risk for developing mammary cancer. 125 female Sprague-Dawley rats were randomly assigned to groups of 11-12 rats and received high or low doses of BBP (0.5 or 5.0mg/kg), PFOA (0.01 or 0.1mg/kg), or Zer (0.01 or 0.1mg/kg), individually or in dual/triple combinations of low doses, via gavage throughout their pubertal period (21-42 days of age) in a controlled environment. The control group received sesame oil.

At 100 days of age, rats were euthanized, and their mammary glands were collected and processed for immunohistochemical staining with antibody anti-Ki67 (1:200 dilution, Clone SP6, Thermo Scientific, Cat# RM-9106-S0), a proliferation marker. A target of 60,000 mammary structure epithelial cells from each animal were analyzed for percentage of Ki67 expression. ANOVA test did not indicate any statistically significant differences among groups. However, when we performed t-tests of individual groups versus control, BBP at high and low doses resulted in a slight but statistically significant (p-values 0.01 and 0.02 respectively) decrease in proliferation rate. As an effect of BBP exposure, the within group variation was significantly lower than in the other groups. This tendency towards lower proliferation is in line with epidemiological studies in humans which reported a negative or lack of association between BBP metabolite levels and breast cancer. When the proliferation evaluation was performed on animals at 50 days of age, no differences were observed between the exposed animals and the control. Our data showed that BBP exposure during puberty induced a slight decrease in the mammary epithelial cell proliferation, suggesting that this compound would not increase the risk of carcinogenesis, while PFOA and zeranol did not show any effect.

(Supported by the NIEHS/NCI grant U01 ES026130 and NCI/NIH Cancer Center Support Grant P30 CA006927)

#29: Effects of perinatal exposures to propylparaben, an estrogenic chemical, on mammary gland development in the mouse

Shirazi AR, Lim IH, and Vandenberg LN

Purpose: Endocrine disrupting chemicals (EDCs) are widespread in consumer products. Some EDCs including propylparaben (PP), a common antimicrobial agent used in packaged foods and personal care products, mimic estrogen. Studies of diethylstilbestrol, DDT, BPA, and other estrogenic EDCs have shown that the prenatal mammary gland (MG) is sensitive to estrogens. This project aims to determine whether exposure to PP during gestation and perinatal development alters postnatal mammary gland growth in mice. We hypothesize that PP will induce sex- and age-specific alterations in growth parameters of the MG.
Methods: Pregnant mice were exposed to vehicle (oil) or one of three doses of PP from mating through weaning. Mammary glands were collected from offspring at postnatal day (PND) 21 (prior to the onset of puberty) and PND 32-35 (the height of puberty). Using a dissection microscope, we analyzed growth parameters in the MG of both male and female offspring.
Results: At PND21, we measured ductal area, ductal extension and number of branching points in females. Ductal area, number of branching points, and number of ductal trees was measured in males. We found sex-specific effects of PP on growth parameters prior to the onset of puberty. These same endpoints, plus measurements of terminal end bud (TEB) development were measured in pubertal females; measurements included total TEB area, TEB density, average TEB size, and total number of TEBs. There were no effects of PP on MG growth parameters in females at puberty, perhaps due to the large variation present at this age.
Conclusions: These results suggest that the mouse MG is affected by perinatal exposures to PP, consistent with the effects of other estrogenic chemicals. Additional study is needed to better evaluate the effects of PP on other endpoints including expression of hormone receptors, proliferation, and gene expression. However, these initial results may suggest that exposures to PP during development could alter risk for mammary disease.

(Supported by the Great Neck Breast Cancer Coalition and NIEHS/NCI grant U01 ES026140.)

Other

#30: Airborne PAH and long term body size in a cohort of African American and Hispanic women in Northern Manhattan

Zeinomar N, Kehm RD, White M, Herbstman JB, Tehranifar P, Perera FP, Miller RL, Terry MB

Purpose: Polycyclic aromatic hydrocarbons (PAH) are widespread environmental pollutants with disproportionately high exposure in urban low income and/or communities of racial and ethnic minorities. Higher concentrations of PAH have been associated with more frequent childhood obesity, however, the presence of PAH-associated obesity in adults still needs to be elucidated.

We assessed the association of PAH exposure during pregnancy and long term measures of body size up to 18 years post-partum in women enrolled in Columbia's Children Center for Environmental Health (CCCEH) birth cohort.
Methods: African-American and Hispanic women in the Bronx or Northern Manhattan, New York (1998-2006) were enrolled during pregnancy and followed up to 18 years post-partum. We examined PAH exposure through women's personal air monitoring in the third trimester of pregnancy. Weight, height, waist circumference, hip circumference, and body fat percentage were measured at 11-18 years post-partum (n=175) and women completed questionnaires about their cancer history, pregnancy history, and other covariates during these follow up visits. We analyzed the sum levels of eight airborne PAH as a log-transformed continuous variable and as a categorical variable by tertiles. We used linear regression models to examine the association of PAH exposure during pregnancy and outcomes (body mass index (BMI), waist-to-hip ratio (WHR), body fat percentage, and change in BMI from pre pregnancy to up to 18 years post-partum).
Results: The mean pre-pregnancy BMI, follow-up BMI, difference in BMI, body fat percentage, and WHR were 25.8 kg/m2, 30.8 kg/m2, 4.4, 36.3%, and 0.78, respectively. We did not find significant associations between airborne PAH measures during pregnancy and any of the long-term body size measures. Although statistically non-significant, one unit increase in log PAH was associated with a 1.02 (95% CI: -0.73 - 2.77) increase in BMI after adjusting for race/ethnicity, parity, breastfeeding, and household income at the time of pregnancy.
Conclusions: This preliminary analysis suggests that there is no association between airborne PAH exposure during pregnancy and long-term body size constructs in African-American and Hispanic women.

(Supported by the NIEHS/NCI grant U01 ES026122.)

#31: Meat and fish preparation methods and risk of breast cancer by estrogen receptor status in the Carolina Breast Cancer Study (CBCS)

Omofuma O*, Steck S, Troester M, Olshan A

Purpose of the Study: Meat prepared at high temperatures contains heterocyclic amines and polycyclic aromatic hydrocarbons which are implicated in breast carcinogenesis. Studies on the association between meat and breast cancer by hormone receptor status are limited, and some show contrasting associations. The study examined the associations between various meat and fish preparation methods and breast cancer by estrogen receptor (ER) status using the Carolina Breast Cancer Study (CBCS) Phase 2.
Methods: The study enrolled women aged 20-74 years with a first diagnosis of invasive or in situ breast cancers. Controls (without breast cancer) were identified through the DMV and Medicare lists and were frequency matched to cases by race [African American (AA) and European American (EA)] and age group. The analytic sample size included 1200 controls, and 701 ER-positive and 475 ER-negative breast cancer cases. Preparation methods and intake frequencies of meat and fish were obtained via questionnaire. Multinomial logistic regression was used to assess the associations of frequency of intake of meat and fish cooked by various preparation methods with breast cancer by ER status.
Results: Compared to no reported meat intake, positive associations were observed for intakes of pan-fried/oven-broiled beef steak one or more times per week for ER-positive breast cancer (OR: 1.33; 95% CI: 1.01, 1.76) and for ER-negative breast cancer (OR: 1.46; 95% CI: 1.07, 1.98). Inverse associations were observed for pan-fried fish intake one or more times per week, (OR: 0.73; 95% CI: 0.55, 0.98) in ER-positive breast cancer. An inverse association also was observed for ER-negative breast cancer, though the confidence interval included the null value (OR: 0.77; 95% CI: 0.55, 1.08). No substantial associations were observed for intake of chicken prepared by pan-frying, oven-broiling, or grilling/barbecuing or for processed meats, such as bacon, sausage, or hot dogs, in relation to breast cancer for either ER subtype.
Conclusion: A positive association with pan-fried/oven-broiled beef and inverse association with pan-fried fish was apparent for both ER-positive and ER-negative breast cancer. The study results do not support a differential effect of these dietary exposures on ER subtypes.

(Supported by the grant GTDR17500160)

*Indicates a recipient of a travel scholarship

#32: Inflammatory Breast Cancer in a husband and wife: The importance of environmental triggers

Veneroso C, Levine PH, van Golen K, Bondy M

Purpose: Report two pilot studies to investigate possible environmental triggers for inflammatory breast cancer (IBC) occurring in a husband wife.
Methods: A woman developed IBC in her right breast shortly after being scratched in the area by her cat. Five years later her husband developed IBC. All experiments were performed using FFPE tissue blocks of resected tumor. The first study at UDel analyzed TLR4 expression using total RNA isolated from the tissue blocks from 16 IBC patients including the husband and wife, 14 non-IBC breast cancer patients and 10 normal breasts. These samples were quantified via qRT-PCR. The second study at Baylor investigated virome studies utilizing coded biospecimens from the husband and wife and four IBC controls. The samples underwent total nucleic acid extraction, library construction, and sequencing on the HiSeq platform (Illumina). Assembled sequence reads were mapped to a custom viral genome database.
Results: TLR4 expression was consistently and significantly higher in all 16 IBC specimens as compared to normal breast and non-IBC tumors. There was no difference between the samples from the husband and wife and the other IBC patients. In virome studies, sequencing of tumor tissues revealed differences between the husband and wife vs. the 4 non-cluster IBC controls. The 4 IBC controls were positive for viral DNA, with up to 6 viruses/sample. Identified viruses were predominantly bacteriophage, including phage for Escherichia, Staphylococcus, and Priopionibacterium.
Conclusions: The TLR4 studies, a marker of infectious processes often seen in response to gram-negative bacteria, suggest that an infectious agent is closely associated with IBC vs. non-IBC breast cancer and normal breast. The phage studies suggest a different mechanism for triggering IBC in the husband and wife than in other IBC patients. The phage we observed target bacteria previously reported in IBC. The IBC Registry repository of more than 100 tissue blocks from IBC patients, including the husband and wife pair, are available to investigators who may have more sensitive and specific assays leading to the identification of infectious, chemical or genetic markers of IBC pathogenesis

#33: Mining high-throughput in vitro testing data to inform in vivo studies of BCERP chemicals

De La Rosa VY, Rudel RA

Advances in high-throughput and high content screening technologies have generated large amounts of in vitro toxicity data for thousands of chemicals. Efforts are on-going to integrate these data with existing toxicological and physiochemical information through online tools and databases. We aim to highlight the potential of these data rich resources, specifically ToxCast and IVIVE tools to prioritize chemicals for further evaluation and inform in vivo studies. We examined the biological activity of 23 BCERP chemicals in the ToxCast high-throughput testing database including PAHs, perfluorinated compounds (PFAS), flame retardants (FR), phthalates (Pth), bisphenol alternatives (BP), benzophenone-3, propylparaben and zeranol. All BCERP chemicals had data from ToxCast high-throughput toxicity assays. The widespread endocrine disruptors, BPA, dibutyl phthalate and PFOA were tested in the greatest number of assay endpoints (>1000), however benzo[a]pyrene was the most biologically, with 50% of active hits across 100 assay endpoints tested. Enrichment analysis revealed that overall, BCERP chemicals had significant enrichment of estrogen receptor (ER) activity, but also androgen receptor (AR) antagonism. ER agonsim by zeranol was the most sensitive endpoint (lowest AC50) across BCERP chemicals with an AC50 of 16pM. The role of zeranol estrogenicity in mammary gland development can be further evaluated by looking at differential expression of ER regulated genes in BCERP transcriptomic studies. For many of the remaining BCERP chemicals, the most sensitive endpoint was not ER related. Antagonism of the constitutive androstane receptor (CAR) by bisphenol AF had an AC50 of 340pM. BPA induction of the xenobiotic enzymes CYP1A1 and CYP1A2 had AC50s of ~5nM. PAHs exhibited significant AhR activity, which is consistent with what is known about this class of chemicals, but also exhibited AR antagonism and mitochondrial toxicity. Work is on-going using the IVIVE tool to integrate internal dose measurements derived from NHANES data to prioritize and evaluate these biological activities in the context of relevant exposure levels.

These results suggest that steroid hormone receptors, specifically AR, AhR and CAR, may also play important roles in mediating chemical effects on mammary gland and breast cancer development, and merit further investigation in on-going BCERP studies.

(Supported by the NIEHS/NCI grant U01 ES026127.)

#34: Prediction of Acute Toxicity and Carcinogenicity of Chemicals using Machine Learning Model

Limbu S, Zakka C, Wathieu HT, Issa NT, Byers SW, Dakshanamurthy, S

The relative contribution of chemicals (including environmental chemicals, drugs, metals, air pollutants, industrial chemicals, environmental carcinogens) toxicity and mechanisms and genetic susceptibility in the etiology of cancer is poorly understood. The experimental testing of toxicity is resource intensive and time consuming. Computational toxicity prediction is an alternative to the conventional tests on animal models. In this study, to predict the toxicity of chemicals, several deep learning models were built on the datasets obtained from US NLM ChemIDplus, Toxin Target database (T3DB), Environment Protection Agency (EPA), EPA Tox21 Challenge, and Carcinogenic Potency Database (CPDB). The performance of our deep learning models was compared with models built using other machine learning algorithms including random forest (RF), Bagging, AdaBoost, and support vector machine (SVM). A highly generalized model with high predicting capability was achieved for the rat and mouse acute oral toxicity dataset from US NLM. The deep learning model gave the best performance with average accuracy of 84.15%, the average AUC of 0.888, the average sensitivity of 0.609 and the average specificity of 0.93. The model predicted with an average accuracy of 73.29 % and average AUC of 0.766 for the rat acute oral toxicity dataset from national toxicology program (NTP) used as external validation dataset. The model built on CPDB data predicted with 63.33% accuracy and .687 sensitivity. Taken together, our modified deep learning models has wide applicability in the prediction of animal toxicity (LD50), carcinogenicity, and toxicity of chemical mixtures, and those studies are in progress.

Our machine learning model now a part our carcinogen mechanistic toxicity prediction method Tox-Can, and generalized toxicity prediction method called CPTM.

(Supported by the DOD grant CA140882.)

#35: Applying Network Analysis to Understand Trends in Collaboration within the Breast Cancer and Environment Research Program (BCERP) Consortium

Bird JE, Arroyo NA, Lindberg S

Purpose: The overarching goal of the Breast Cancer and the Environment Research Program (BCERP) is to support integrated scientific research to enhance understanding of environmental and genetic factors underlying breast cancer risk throughout the lifespan. Team science is an integral aspect of the transdisciplinary consortium and this study aims to understand and predict established and growing networks of collaborative work.
Methods: In this evaluation study, we apply the methods of social network analysis to better understand longitudinal trends in collaboration and scientific integration within the BCERP Consortium. Specifically, we examine the growth and proliferation of collaborations among BCERP investigators and affiliates, which for the purpose of this initial analysis are defined as co-authorship of publications. Collaborative networks evaluated for the 3 BCERC Centers, 14 Puberty Studies, 9 Windows of Susceptibility sites, 3 Communications sites, and 2 Coordinating Centers, between 23 principal sites from 2003-present.
Results: Initial findings identify collaborative clusters within the BCERP Consortium, including some that span institutional and disciplinary boundaries. Findings also provide some preliminary evidence of the Consortium's transdisciplinary nature and productivity. The total number of collaborative publications was 50 across this time period, starting in 2007. The number of collaborations was 1 within the first grant cycle (2003-2010), 27 within the following cycle after incorporating WOS sites (2011-2015), and 22 within the current cycle (2016-2018). For the BCERP Centers, the number of publications increased after the grant period (2003-2010), on average, by 23times. 86.2% of the Puberty Studies publications were collaborative during their grant period (2003-2015) and continue to produce collaborative work after this period.

Conclusions: With the increase in publications shown from earlier cycles, it is feasible to predict an increase in collaborative work during and after the grant periods. These results provide a foundation for future work that includes a more comprehensive picture of collaborative activity, such as collaboration on grants, scholarly presentations, lay publications, and other dissemination products.

(Supported by the NIEHS/NCI grant U01 ES026127.)

#36: Perfluorooctanoate and Insulin Resistance in Young Girls in Greater Cincinnati

Fassler CS, Xie C, Biro FM, Schwartz RC, Pinney SM

Purpose: Perfluorooctanoate (PFOA) is widely used in both commercial and household products. Studies have shown the association of higher PFOA levels in humans with adverse health effects. Specifically, higher PFOA levels are associated with lower body mass in infants and children. We hypothesized that in young girls this association between PFOA and body mass results in a decrease in insulin resistance.
Methods: In 2005-2006, we conducted a cross-sectional study of environmental biomarkers and insulin resistance in 6-7 year-old girls from Greater Cincinnati (n=353). Participants provided blood samples to measure polyfluoroalkyl substances (PFAS), fasting insulin and glucose in serum. Clinical exams included anthropometric measurements and pubertal maturation staging. Linear regression and mediation analyses, specifically structural equation modeling (SEM), were used to determine the strength and direction of the relationships between PFAS, pubertal maturation status, waist-to-height ratio, body mass index (BMI), and insulin resistance.
Results: The mean insulin (12.44 g/mL) and glucose (84.8 mg/dl) were within the reference values. The median PFOA (7.7ng/ml) was twice the National Health and Nutrition Examination Survey (2005-2006). Only PFOA, of the PFAS, showed statistically significant relationships with the outcomes. In regression models, PFOA (1 log normal unit) was significantly associated with decreased BMI and waist-to-height ratio (β=-0.3269, p=0.0008; β=-0.0079, p=0.0343), and somewhat associated with a decrease in the HOMA Index of insulin resistance (β=-0.1025, p=0.0864). In SEM, PFOA retained an inverse relationship with BMI (β=-0.398, p=0.000) and HOMA (β=-0.066, p=0.221), though the relationship with HOMA was no longer statistically significant. SEM also shows early breast maturation (Tanner breast or pubic stage 2 or greater) and BMI were statistically associated with increased HOMA Index (β=0.203, p=0.008; β=0.155, p=0.000).
Conclusions: These findings suggest PFOA exposure in young girls affects both BMI and ultimately insulin resistance. Mediation analysis shows that once puberty is added to the model, the direct effects of PFOA on insulin resistance dissipate and that puberty is an effect modifier between BMI and insulin resistance.

(Supported by the HHS/NIH/NCRR grant UL1 RR026314, the NCI/NIH grant P30 ES006096, and NIEHS/NCI grants U01 ES12770, U01 ES019453, U01 ES026119.)

#37: Effects of high fat diet and oxybenzone on tumor vascularity

Morozova O, Haslam SZ, Schwartz RC

Purpose: Our previous studies found that a diet high in saturated animal fat diet (HFD) increased incidence of Trp53-null mammary tumors. Notably, pubertally restricted HFD promoted tumorigenesis in adulthood. Irrespective of life stage exposure, HFD resulted in tumors showing increased proliferation, vascularity, and macrophage recruitments. Oxybenzone (benzophenone-3, BP-3), an ingredient in sunscreen and many personal care products is a putative endocrine disrupting chemical that may alter mammary gland development, and thus influence mammary tumorigenesis. We are studying the interactions between HFD and BP-3 exposure during puberty and adulthood, and its influence on tumorigenesis. Here, we present the effects of HFD and BP-3 on tumor vascularity.
Methods: Mammary gland fragments from 8-week-old Trp53-null mice were transplanted to cleared inguinal fat pads of 3-week-old BALB/c mice. Mice were divided into 6 groups and fed the following diets:
1 and 2) low fat diet (LFD; 10% kcal fat) +/- BP-3
3 and 4) HFD (60% kcal fat) switched at 10 weeks of age to LFD +/- BP-3 for the entire period
5 and 6) LFD switched at 10 weeks of age to HFD +/-

BP-3 for the entire period. The BP-3 dosage resulted in urine excretion of between 2 and 5 mg/kg body weight/5 days, similar to human BP-3 excretion after heavy topical application (Gonzalez et al., Brit. J. of Dermatol., 2006). Tumors were collected and histopathological types identified: spindle cell tumors and epithelial tumors, the latter comprising solid, cribriform, glandular, and acinar carcinomas. Spindle cell and epithelial tumors of the various treatment groups were sectioned and immunohistochemically stained for CD31, an endothelial cell marker of vascularization.

Results: Images were captured at 40X magnification and overlaid with grids containing 240 squares (324 μ m2/square). CD31-positive squares were enumerated and vascularity expressed as the percentage of CD31-positive squares. Quantitation is ongoing. We will present quantitations of BP-3 and HFD effects on tumor vascularity in the different treatment groups.

Conclusions: Alterations in tumor vascularity will be discussed in the context of tumor growth properties (see abstract by Kariagina et al.) and tumor gene expression (see abstract by Xie et al.).

(Supported by the Breast Cancer and the Environment Research Program Grant U01ES026119 from the National Institute of Environment Health Science (NIEHS) and the National Cancer Institute (NCI), NIH, DHHS)

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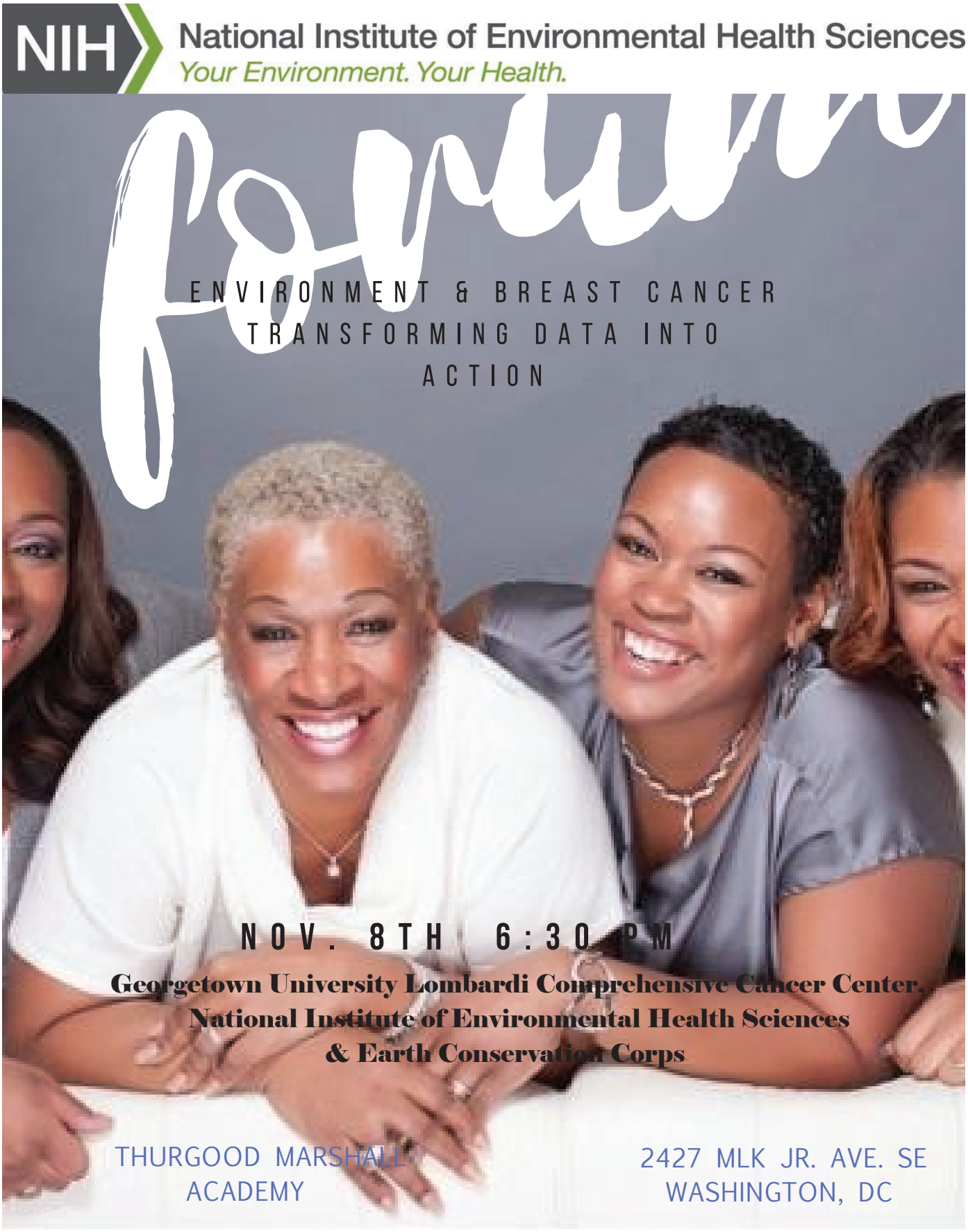

NIH
National Institute of Environmental Health Sciences
Your Environment. Your Health.
forum
ENVIRONMENT & BREAST CANCER
TRANSFORMING DATA INTO
ACTION
NOV. 8TH 6:30 PM
Georgetown University Lombardi Comprehensive Cancer Center,
National Institute of Environmental Health Sciences
& Earth Conservation Corps
THURGOOD MARSHALL
ACADEMY
2427 MLK JR. AVE. SE
WASHINGTON, DC

Local Restaurant Suggestions

Epicurean and Company
0.1 Miles from Georgetown University Hotel
3800 Reservoir Rd NW, Washington, DC 20007
"Eclectic eatery on university campus has sushi, hibachi, a salad bar, pizza & more, plus TV sports."
Phone: (202) 625-2222
Open 24 Hours
http://www.epicureanandco.com

The Tombs
0.5 Miles from Georgetown University Hotel
1226 36th St NW, Washington, DC 20007
"Veteran university haunt in converted 19th-century townhouse serving comfort fare, brews & pub grub."
Phone: (202) 337-6668
Hours: 11:30 am- 1:30 am
http://www.tombs.com/

1789 Restaurant
0.5 Miles from Georgetown University Hotel
1226 36th St NW, Washington, DC 20007
"A luxe, renovated Federal house sets the scene for refined seasonal American fare."
Phone: (202) 965-1789
Hours: 5:00 pm - 10:00 pm
https://www.1789restaurant.com

Saxbys Georgetown
.5 Miles from Georgetown University Hotel
3500 O St NW, Washington, DC 20007
"Relaxed coffeehouse chain offering small-batch coffees & light fare such as sandwiches."
Phone: (202) 338-3777
Hours: 6:00 am – 10:30 pm
http://www.saxbyscoffee.com

Patisserie Poupon-Georgetown DC
0.7 Miles from Georgetown University Hotel
1645 Wisconsin Ave NW, Washington, DC 20007
"Croissants, macarons, cakes & sandwiches in a cozy, French-inspired cafe with a coffee bar & patio."
Phone: (202) 342-3248
Hours: 8:30 am – 6:00 pm
http://www.patisseriepoupon.net

Jetties
0.7 Miles from Georgetown University Hotel
1609 Foxhall Rd NW, Washington, DC 20007
"Sandwiches on artisanal bread & tossed-to-order salads in family-friendly space with outdoor seats."
Phone: (202) 380-9298
Hours: 11:00 am – 8:00 pm
https://jettiesdc.com/

Café Bonaparte
0.7 Miles from Georgetown University Hotel
1522 Wisconsin Ave NW, Washington, DC 20007
"Cozy French cafe with sidewalk seating serving crêpes, bistro fare, coffee, wine & more."
Phone: (202) 333-8830
Hours: 9:00 am – 10:00 pm
https://www.cafebonaparte.com/

Martin's Tavern
0.8 Miles from Georgetown University Hotel
1264 Wisconsin Ave NW, Washington, DC 20007
"Popular tavern serving American eats in both a cozy interior with wooden booths & outdoors."
Phone: (202) 333-7370
Hours: 11:00 am – 1:30 am
http://www.martinstavern.com

Bistrot Lepic & Wine Bar
0.8 Miles from Georgetown University Hotel
1736 Wisconsin Ave NW, Washington, DC 20007
"Rustic spot features traditional French fare downstairs, plus a wine bar upstairs."
Phone: (202) 333-0111
Hours: 11:30 am – 2:30 pm, 5:30 pm – 9:30 pm
http://www.bistrotlepic.com

Peacock Café
0.9 Miles from Georgetown University Hotel
3251 Prospect St NW, Washington, DC 20007
"American dishes (brunch too) & a varied wine selection in a sleek space with outdoor seating."
Phone: (202) 625-2740
Hours: 11:00 am – 10 pm
http://www.peacockcafe.com/

Attractions

C&O Canal
1.2 Miles from the Georgetown University Hotel
1057 Thomas Jefferson Street NW Washington, DC 20007
"Bike, run, or stroll down the paths lining the beautiful Chesapeake & Ohio Canal."
Phone: (202) 653-5190
Visitor center hours: Wed- Sun. 9:30 am-4:30 pm
https://www.nps.gov/choh/index.htm

Georgetown waterfront park
1.4 Miles from the Georgetown University Hotel
3303 Water Street NW, Washington, DC 20007
"Georgetown Waterfront Park is a scenic urban park that stretches along the Potomac waterfront."
Hours: daylight hours
https://georgetownwaterfrontpark.org/

Dumbarton Oaks Gardens and Museum
0.9 Miles from Georgetown University Hotel
1703 32nd Street NW, Washington, DC 20007
"Dumbarton House is a historic house museum owned by The National Society of The Colonial Dames of America. With an eclectic collection of furniture, paintings, and ceramics, visitors learn about what life was like in Washington during the early 19th century."
Phone: (202) 339-6400
Museum Hours: 11:30 am -5:30 pm
Garden Hours: 2:00-5:00 pm
Admission: Free
https://www.doaks.org/visit

French Embassy
0.5 Miles from Georgetown University Hotel
4101 Reservoir Rd NW, Washington, DC 20007
"Enjoy all things French at the French Embassy located across the street from the hotel on Reservoir Rd. NW. There are special events, movies and tours that take you to the beauty of all things French."
Phone: (202) 944-6195
Hours: Monday-Friday 8:45 am-12:30 pm, 2-5 pm
https://franceintheus.org/

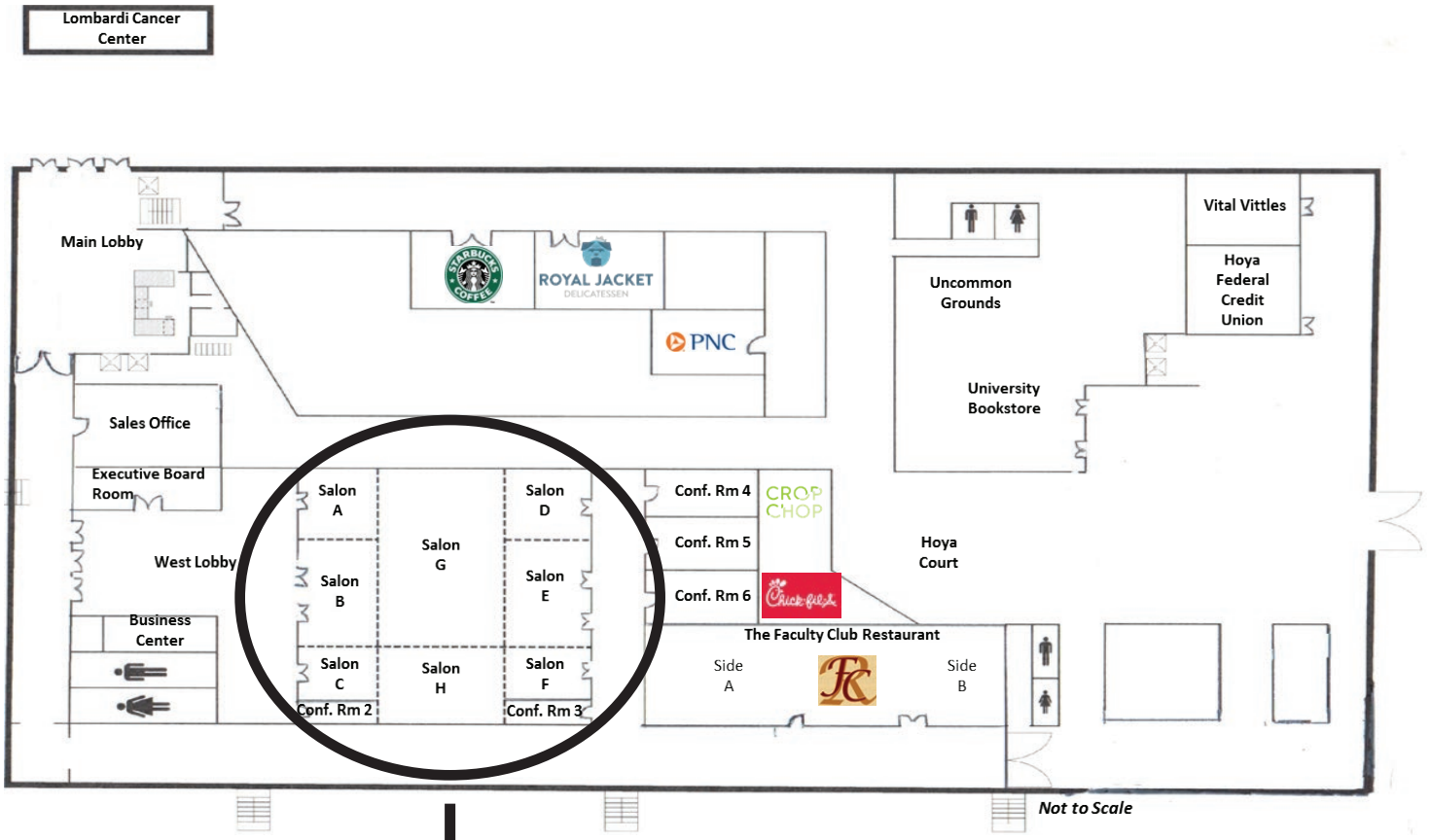
The Shops at Georgetown Park
1.3 Miles from Georgetown University Hotel
3222 M Street, NW, Washington, DC 20007
Phone: (202) 965-1280
Hours: 10:00 am-8:00 pm
http://www.georgetownpark.com/

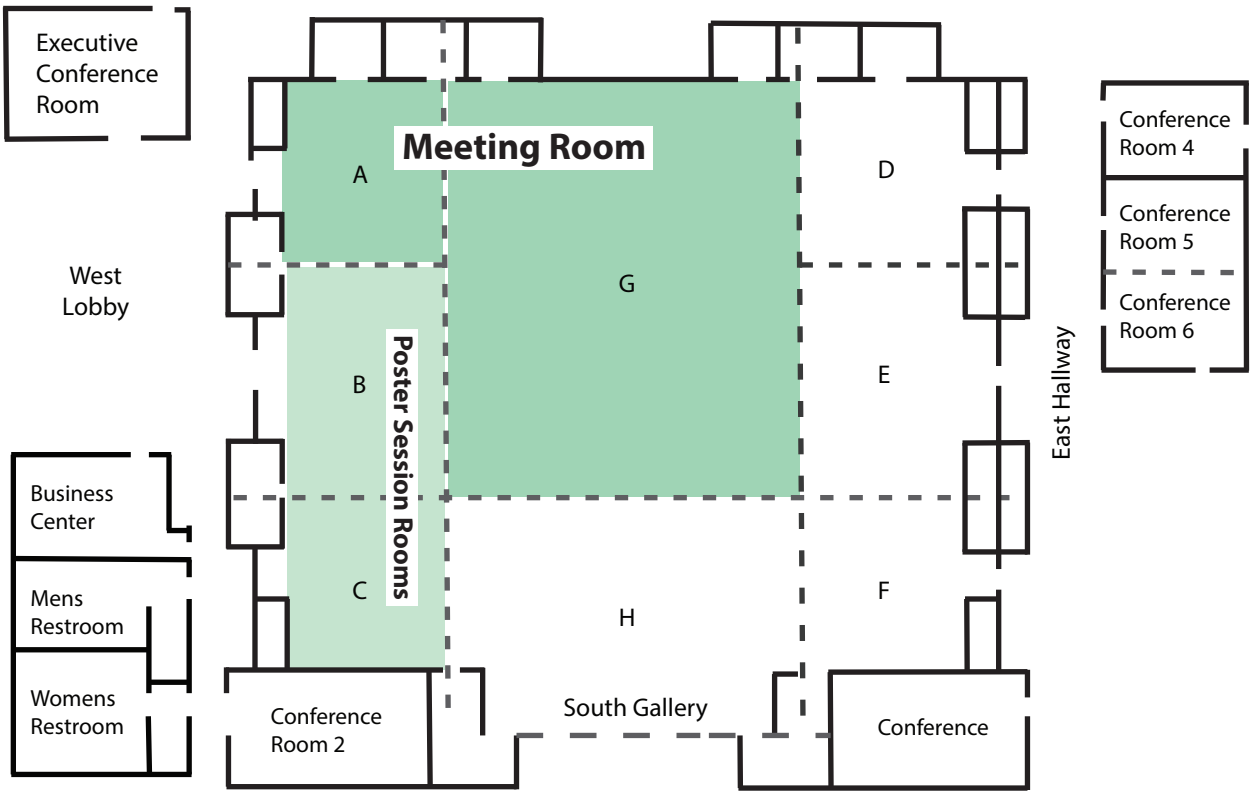
Tudor Place
1.1 Miles from Georgetown University Hotel
Tudor Place, 1644 31st Street NW, Washington, DC 20007
"This historic landmark has been a fixture in DC since 1816, serving as a home to descendants of Martha Washington for six generations. Inside the elegant house, discover furnishings, household items and fascinating Washington-related artifacts. The five-plus acres worth of gardens on the estate make for a wondrous and scenic outdoor experience."
Phone: (202) 965-0400
Hours: 10:00 am – 4:00 pm
House Tours Admission: $10
Self-Guided Garden Tour Admission: $3
https://www.tudorplace.org/plan-your-visit/hours-directions/

John F. Kennedy Center for the Performing Arts
2.5 Miles from Georgetown University Hotel
2700 F Street NW
Washington DC 20566
"The world-renowned Kennedy Center has Broadway shows, operas, symphonies and ballets but there are also free concerts every night at 6pm on the Millennium Stage. Arrive early and take a tour!"
Phone: (202) 467-4600
Tour Hours: 10:00 am – 5:00 pm
Free Show at 6:00 pm
http://www.kennedy-center.org/pages/visitor/tours

Old Stone House
1.1 Miles from the Georgetown Hotel
3051 M Street NW, Washington, DC 20007
"Old Stone House, built in 1765, is the oldest known private home in Washington, DC. The National Park Service maintains the property and it is open to the public."
Phone: (202) 426-6851
Hours: Noon – 5:00 pm
Free Admission
https://www.nps.gov/nr/travel/wash/dc17.htm

Georgetown University Hotel & Conference Center Map





Georgetown University Map

ACADEMIC – CAMPUS BUILDINGS

- 34 Admissions
- 39 Bookstore
- 35 Bunn Intercultural Center (ICC)
- 2 Car Barn
- 29 Dahlgren Chapel of the Sacred Heart
- 23 Gervase Building
- 27 Healy Hall
- 14 Healey Family Student Center
- 45 Heating and Cooling Plant
- 46 Heyden Observatory and Ecology Lab
- 7 Institute for the Study of Diplomacy
- 12 Lauinger Library
- 39 Leavey Center
  - Sellinger Lounge
  - Bookstore
- 26 Maguire Hall
- 6 Mortara Building
- 30 New North
- 28 Old North
- 10 Poulton Hall
- 41 Rafik B. Hariri Building
  - McDonough School of Business
- 11 Reed Alumni Residence
- 38 Regents Hall
- 36 Reiss Science Building
- 22
  - John Main Center
- 32 Ryan Administration Building
- 52 St Mary's Hall
- 8 Wagner Alumni House
- 3 Walsh Building
- 34 White-Gravenor Hall
  - Undergraduate Admissions
- 16 Wolfington Hall
  - Jesuit Residence

CONFERENCE / AUDITORIUMS

- 35 Bunn Intercultural Center (ICC)
- 33 Copley Formal Lounge
- 32 Davis Performing Arts Center
  - Gonda Theatre
- 27 Gaston Hall
- 40 **Georgetown University Hotel and Conference Center**
- 41 Lohrfink Auditorium
- 19 McShain Lounge
- 30 McNeir Auditorium
- 65 New Research Building Auditorium
- 27 Riggs Library
- 67 Warwick Evans Conference Room
- 62 W. Proctor Harvey Clinical Teaching Amphitheater

RESIDENCE HALLS

- 9 Alumni Square
- 33 Copley Hall
- 51 Darnall Hall
- 24
- 31 Harbin Hall
- 50 Henle Village
- 18 Kennedy Hall
- 1 Loyola Xavier Ryder Hall (LXR)
- 19 McCarthy Hall
- 4 Nevils Hall
- 14 New South Hall
- 37 Pedro Arrupe, S.J. Hall
- 17 Reynolds Hall
- 25 Ryan Hall
- 13 Village A
- 21 Village C East
- 20 Village C West

TRANSPORTATION

- Capital Bikeshare
- Car2Go
- Circulator
- GUTS
- Metrobus
- Mini Shuttle
- Ride Share (Uber, etc)
- Taxi
- Zipcar

HOSPITAL & PATIENT CARE

- 59 Concentrated Care Center (CCC)
- 55 Gorman Building
- 53 Kober-Cogan Building
- 58 Lombardi Comprehensive Cancer Center
- 56 Marcus J. Bles Building
- 57 MedStar *Georgetown University Hospital*
- 54 Pasquerilla Healthcare Center (PHC)

ATHLETIC DEPARTMENTS

- 42 Cooper Field
- 43 John R. Thompson Jr. Intercollegiate Athletic Center
- 47 Kehoe Field
- 44 McDonough Arena
- 49 Shaw Field
- 48 Yates Field House

VISITOR INFORMATION

Visitor Parking
Southwest Quad parking garage
- Entrance from Canal Rd NW

Leavey Center parking garage
- Entrance from Reservoir Rd NW

For campus emergencies, please contact the **Georgetown University Police Department at 202-687-4343**

Accessible Entrance
Historic buildings and many hills on campus make some paths difficult to navigate.
Follow ··· *Access Path* signs for accessible routes through campus. Some routes utilize building elevators.

····· Shared Pedestrian/Bike Route
—— Shared Bike/Vehicle Route

MEDICAL CENTER

- 64 Basic Science Building
- 67 Building D
- 60 Dahlgren Medical Library
- 63 Med-Dent Annex
- 62 Med-Dent Building
- 65 New Research Building
- 61 Pre-Clinical Science Building
- 66 Research Resource Facility (RRF)
- 52 St. Mary's Hall

DINING

- 14 Bulldog Tavern
- 51 Epicurean and Company
- 39 Hoya Court
- 15 O'Donovan Dining Hall (Leo's)
  - *Open to the public*
- 5 Tombs/1789

2018 BCERP Annual Meeting Program At a Glance

Detailed program agenda on pages 5-8

Thursday, November 8

7:00-8:00 a.m. Registration

8:00-8:15 a.m. **Welcome and Introduction of Keynote Speaker – Salon AG**

8:15-9:00 a.m. **Keynote Address – Salon AG**
Research directions: the environment, windows of susceptibility, and breast cancer

9:00-10:30 a.m. **Session 1: Windows of Susceptibility – Salon AG**
- Summary of target cells changes during windows of susceptibility for breast cancer
- Environmental exposures during key windows of breast susceptibility
- Effect of pubertal exposure to mixtures on mammary gland gene expression
- Obesity, progenitor cells, and postmenopausal breast cancer

10:30-10:45 a.m. Break

10:45 a.m.-12:15 p.m. **Session 2: Endocrine Disruption and Breast Cancer Risk – Salon AG**
- Hormone-like effects of metals and metalloids
- Chemical mixtures from fracking and altered mammary gland development
- Epigenetic changes in blood as biomarkers of exposure
- Reporting environmental exposures to study participants and lay people

12:15-1:30 p.m. **Two concurrent lunchtime sessions** - Lunch is provided
- **Environmental Health Research Opportunities in *All of Us* – Salon AG**
- **NCI Training Opportunities and Career Development – Salon DE**

1:45-3:15 p.m. **Poster Session – Salon BC**

3:15-3:30 p.m. Break

3:30-5:00 p.m. **Session 3: New Emerging Concepts of Environmental Exposures and Risk of Developing Breast Cancer – Salon AG**
- Serum concentrations of persistent organic pollutants (POPs) and mammographic breast density in a highly exposed population in Triana, Alabama
- Paternal environmental exposures in the pre-conception window and programming of breast cancer in daughters
- Xenoestrogens cause estrogen receptor-dependent R-loop formation and DNA damage
- Elucidating the effects of polybrominated diphenyl ether (PBDE) on mouse mammary glands through single-cell RNA sequencing analysis

5:30 p.m. **Shuttle bus leaves the Georgetown Conference Center for the Community Forum**

6:30-8:30 p.m. **Community Forum** – Thurgood Marshall Academy Public Charter School

Friday, November 9

7:30-8:30 a.m. Registration

8:30-10:00 a.m. **Session 4: Breast Cancer and Environmental Exposures Beyond Classical Endocrine Disrupting Chemicals – Salon AG**
- The interaction of lifestyle with a putative EDC: high fat diet and BP-3
- Social isolation and breast cancer recurrence
- Air pollution exposures and breast cancer risk
- Challenges to increase diverse engagement in environmental health and breast cancer advocacy

10:00-10:15 a.m. Break

10:15-11:45 a.m. **Session 5: Optimal Community Approaches for Environmental Research – Salon AG**
- A community-based navigator approach to BCERP: utilizing outreach and engagement
- Using targeted social media to communicate culturally sensitive and interactive environmental risk information about breast cancer to mothers
- The Health and Environmental Research in Make-up of Salinas Adolescents (HERMOSA) Study
- Development of a data visualization tool to explore occupational chemical exposures among working California women

11:45 a.m.-12:30 p.m. **Announcement of Poster Awards and Closing Remarks by Linda Birnbaum, Director, NIEHS – Salon AG**

12:30 p.m. Meeting Adjourned

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