

## Opening Keynote Address

### Halogenated Flame Retardants: Does the Benefit Justify the Risk?

Linda S. Birnbaum, *National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA*

Brominated flame retardants (BFRs) encompass a broad class of structurally distinct chemicals which have bromine atoms in common. The rapid increase in their use in the last decades of the past century was followed by an increase in their levels in wildlife and in people. This dramatic rise led to a burst in studies concerning the potential for adverse effects in a wide variety of animal species, as well as recently, humans. The majority of these studies focused on polybrominated diphenyl ethers (PBDEs) which were produced commercially as three complex mixtures, known as Penta, Octa, and Deca. While Penta and Octa were banned in the European Union and withdrawn from production in the US in 2004, their environmental persistence is resulting in ongoing exposure to wildlife and people. Deca was banned by the European Court of Justice in 2008, and in several states of the US. However, it remains a high production volume chemical and is used extensively world-wide, especially in Asia. The other major BFRs, tetrabromobisphenol A (TBBPA) and hexabromocyclododecane (HBCD), are not subjected to any regulation. There are many other BFRs, e.g., BTBPE, DBDPE, TBBPA-DBPE, which are now being detected and are unregulated.

The majority of studies of the health effects have been conducted on the PBDEs. In general, the lower brominated congeners (Br<sub>4-6</sub>) are more toxic to invertebrates and to fish than those with more bromines. Only Deca has been tested in 2 year rodent studies and shown to be carcinogenic. Penta and Octa are hepatotoxic and induce xenobiotic metabolizing enzymes. Experimental animal studies, in combination with some *in vitro* experiments, demonstrate that many PBDE mixtures and individual congeners are endocrine disruptors, interfering with estrogen, androgen, and thyroid hormone systems via a multitude of mechanisms. There is growing concern for early life exposure which leads to developmental reproductive toxicity, immunotoxicity, and neurotoxicity. There have been several recent epidemiological studies which have shown associations between maternal PBDEs and cryptorchidism, and adult PBDEs and thyroid levels, decreased sperm quality, diabetes, and metabolic syndrome.

There have been few studies on the health effects of HBCD or TBBPA in humans. However, experimental animal and *in vitro* data have shown that HBCD is a skin irritant at high concentrations, can be hepatotoxic and induce hepatic enzymes, similar to the PBDEs, disrupts thyroid hormones, is a reproductive toxicant, and is developmentally neurotoxic. The biological properties of the distinct stereoisomeric forms of HBCD have just begun to be investigated. Even fewer studies have been conducted *in vivo* with TBBPA, although its structural similarity to the environmental estrogen, BPA, has caused some concern for endocrine disruption. A recent study suggested it might cause hearing deficits. Whether levels in wildlife or people for HBCD or TBBPA approach those of concern for health effects remains to be determined. (This abstract does not reflect NIEHS/NIH policy.)

## Session I: BCERC Findings – Pubertal Maturation in Humans and Animals

### **Interrelationships of Changes in BCERC Girls: What do we know about puberty?**

Frank Biro, *Cincinnati Children's Hospital Medical Center, Cincinnati, OH, on behalf of fellow investigators, staff, advocates, participants and their families*

Puberty represents the physical manifestations of a complex series of events which include neuroendocrine development, changes in body composition and growth parameters, and appearance of secondary sexual characteristics. The presentation will provide a brief description of the BCERC epidemiology project, the baseline and subsequent maturation of the cohort, anthropometric factors associated with onset of puberty, and the inter-relationships of the different pubertal parameters. The pubertal status of the BCERC cohort will be contrasted to data from the PROS study. Longitudinal data using the new analytical approach to sex hormone levels (TLC/MS/MS) will document hormone changes that precede the appearance of secondary sexual characteristics that have not been appreciated with traditional, less sensitive analytic approaches. Finally, anthropometric and hormonal profiles of pathways through puberty will be presented.

## Pubertal Mammary Gland Development: an Animal Model

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Animal and human studies show that the period of pubertal mammary gland development is a time of special sensitivity to environmental exposures that can affect future risk of mammary cancer. Pubertal development is regulated within the mammary gland itself and by the production of factors (hormones, growth factors) produced elsewhere in the body. Thus, alteration of normal pubertal development can occur due to changes in the mammary gland itself, or due to systemic changes affecting other organs in the body, such as the ovaries, that regulate the mammary gland. Understanding normal regulation of pubertal development provides the basis for understanding the mechanisms and potential risk of mammary cancer resulting from alterations in mammary gland development caused by environmental exposures.

In the mouse model, pubertal development of the mammary gland consists of ductal development through ductal elongation and secondary and tertiary ductal branching. Ductal elongation and initial branching begins in specialized structures, terminal end buds (TEBs), and is dependent upon estrogen (E). E induces production of a growth factor, amphiregulin (Areg), in estrogen receptor-containing mammary epithelial cells in TEBs. Areg then acts on stromal cells to induce a second growth factor that acts on mammary epithelial cells to induce proliferation. The role of P in pubertal development has been less studied. We now find that P acting through progesterone receptor A (PRA) also produces Areg and, similarly to E, promotes proliferation in TEBs. This effect of P is E-independent, since it is blocked by an anti-progestin but not by an anti-estrogen. P action has also been implicated in ductal branching. We find that RANKL, induced by P and involved in branching in the adult gland, is also induced by P in ductal cells of the pubertal gland, indicating that P also promotes ductal branching during puberty. We have compared pubertal mammary gland development in two mouse strains (BALB/c and C57BL/6) with different sensitivities to E and P at sexual maturity. We found that during puberty estrogen and progesterone receptor expression is similar, pubertal ductal elongation is similar, and either E or P can upregulate Areg to promote ductal elongation in both mouse strains. However, in C57BL/6 mice, the ductal tree has less overall branching. This is correlated with a lack of RANKL induction by P. Normal pubertal development also requires certain inflammatory processes mediated by tissue macrophages to facilitate the tissue remodeling and angiogenesis that are required for ductal elongation and branching. How these inflammatory processes are regulated was not previously known. We have now determined that P induces inflammatory processes in the mammary gland as evidenced by *in vivo* macrophage recruitment. We hypothesize that P produces these effects through induction of RANKL, a known activator of NF- $\kappa$ B, a regulator of inflammation.

In summary, our findings are consistent with a model of pubertal mammary gland development in which both E and P induce Areg to promote ductal elongation. Additionally, P-induces RANKL to promote ductal branching and normal inflammatory processes required for tissue remodeling needed for mammary gland development. The normal processes of pubertal mammary gland development can be altered by environmental exposures during puberty. This has been shown for diet and certain chemical exposures. Understanding normal regulation of pubertal development provides the basis for understanding the mechanisms underlying the alterations caused by environmental exposures and their potential impact on breast cancer risk.

This work was supported by the Breast Cancer and the Environment Research Centers Grant U01 ES/CA 012800 from the National Institute of Environment Health Science (NIEHS) and the National Cancer Institute (NCI), National Institutes of Health, Department of Health and Human Services.

### **Diet, Phytoestrogens and Pubertal Development in a Multiethnic Cohort of Young Girls**

Lawrence H. Kushi, Sc.D., *Kaiser Permanente, Division of Research, Oakland, CA, on behalf of fellow investigators, staff, advocates, participants and their families*

The Breast Cancer and the Environment Research Centers include collaborative epidemiologic studies that are investigating factors that may be causally associated with early onset of puberty. These studies, conducted in the San Francisco Bay Area, Greater Cincinnati area, and New York City, have enrolled over 1,200 girls who were age 6-8 y during baseline examination. These girls are followed on at least an annual basis to track pubertal maturation and other developmental milestones, and to update information on relevant exposures. It is known from our study and others that there is substantial racial/ethnic diversity in onset of puberty, and that one prominent factor known to influence onset is body size, with higher body mass index associated with earlier pubertal onset.

Because of the importance of body size, factors that influence body size are of great interest in onset of puberty. Among these include food intake and energy expenditure. As the impact of body size on onset of puberty is likely at least in part related to the influence of adiposity on sex hormone metabolism, specific dietary factors such as phytoestrogens may be responsible themselves for direct hormonal effects. This presentation will review some of the basis for suggesting that dietary factors may be important in onset of puberty, and present preliminary findings from the BCERC epidemiologic studies investigating associations of selected dietary factors with onset of puberty. Implications for examining the influence of other hormonally-active agents and breast cancer risk will also be examined.

## Session II: BCERC Findings – Environmental Exposures and Pubertal Maturation

### Detecting Effects on Pubertal Maturation by Weak Environmental Agents in the BCERC Cohort

Mary S. Wolff, Susan Teitelbaum, Susan M. Pinney, Gayle Windham, Lawrence H. Kushi, Frank Biro, Chris Erdman, Robert Hiatt, Manori J. Silva, Xiaoyun Ye, Michael E. Rybak, Christine M. Pfeiffer, Laura Liao, and Antonia M. Calafat and BCERC Project 2 collaborating investigators

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Hormonally active environmental exposures may delay or accelerate the normal timing of puberty, which is fueled by steroid hormones. The Breast Cancer and Environment Research Centers (BCERCs) are investigating environmental exposures and puberty in girls starting at 6 years of age. We hypothesize that hormonally active environmental exposures because of their weak biologic activity may alter age at pubertal onset, although their effects may be modified by adiposity (the major source of prepubertal estrogen) as well as genetic and dietary factors.

The BCERC cohort of 6-8 year old girls is multithnic and geographically diverse. It was established at 3 national BCERC sites starting in 2004. At baseline, urine specimens from 1151 girls were analyzed for biomarker panels of hormonally active chemicals (9 phthalate, 8 phenol, and 3 phytoestrogen metabolites). Breast development stages from physical examination, and covariate information including body mass index (BMI), diet, and selected characteristics were collected. To estimate associations of biomarkers and puberty, we calculated multivariate adjusted prevalence ratios (aPR) for the baseline biomarker measurements in relation to breast and pubic hair stages at first annual follow-up.

We observed some weak effects of the environmental biomarkers on breast stage and modification by diet and adiposity. These findings are of interest to understand potential health effects and to guide additional translation and epidemiologic investigations, including future choices of genetics and biomarkers of reproductive effects. Longer follow-up may provide further insight on effects of weak hormonal agents in relation to female puberty.

## Endocrine Disruptors and the Windows of Susceptibility in the Mammary Gland at Puberty

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There is a growing concern that environmental compounds such as Bisphenol A (BPA) and butyl benzyl phthalate (BBP) which have endocrine disrupting properties, might have potential adverse effects on hormone-sensitive organs such as the breast. These compounds are known to interfere with endocrine systems, affecting hormonal balances that disrupt normal functions and were chosen based in the finding reported in the epidemiological studies. Sprague Dawley rats were exposed to BPA, BBP at different stage (prenatal, prepubertal), at different dose level (low, high), and studied at different age (21, 35, 50, 100). We have found that, in terms of prenatal and prepubertal treatment of rats, exposure to BPA or BBP does not affect body weight, vaginal opening, uterine weight, or estrous cyclicity. Instead we have found that imprinting of genes during early periods of development causes permanent manifestations that are expressed later in life. *Genomic analysis of the rat mammary gland of animals exposed to BPA or BBP prenatally or prepubertally showed that each compound has a unique signature.* Each compound has defined biological processes, cellular components, and molecular functions. The genomic signature in the mammary gland determined by the compound provides specific canonical pathways and networks of gene interaction, the most important of which appear to be transcription- and DNA-related genes, oncogenes, tumor suppressor genes, DNA damage response and repair genes, apoptosis genes, neurotransmitter genes, immunity and inflammation genes, fatty acid and lipid metabolism genes, and cell differentiation and development genes. The aggressive pattern of fat metabolism is more evident for BBP, whereas, BPA does not seem to affect lipid homeostasis. Data suggest that there is an association between obesity and neuroendocrine pathway and fatty acid and lipid metabolism genes with Body Mass Index and breast stage, and the genomic signature of the rat mammary gland of BBP-exposed animals that is characterized by an enrichment of neuroendocrine and fatty acid and lipid metabolism genes. Following genomic analysis, we also concluded that neonatal/prepubertal BPA exposure induces a specific genomic signature in the rat mammary gland that increases its susceptibility to carcinogenesis. The genomic changes induced in the rat mammary gland by BPA or BBP exposure have identified a specific set of genes relevant to humans. As a result of this research, our studies have provided a new set of genomic markers and new paradigms for the understanding of environmental exposure in human. The take home messages are: 1-BPA affects large number of oncogenes that increase the tumorigenic response in the mammary gland to a carcinogenic insult; 2-More studies in human like direct transformation assay of human breast epithelial cells with this compound must be done to determine a cause effect in the cancer event; 3-BBP had a great effect on fatty acids and lipid metabolism genes that might be correlated to obesity and diabetes; 4-Genes with polymorphisms in girls highly exposed to these compounds were mainly related to lipid metabolism and were found in girls with altered body mass index; 5-BBP has a significant effect on immune response and defense genes; 6-The mammary gland is a sentinel of what could happen in other organs in the development of other diseases like obesity, diabetes, eczema and asthma; 7-The genomic effect observed in the mammary gland points toward the need to further the study of this compound in other organ related diseases; and 8-Avoid the exposure of young girls to these compounds. (*This work was supported by NCI and NIEHS Grant UO1 ES012771*).

## Timing of Exposure to Perfluorooctanoic Acid (PFOA) and Benchmarks of Pubertal Maturation

Susan M. Pinney<sup>1</sup>, Gayle C. Windham<sup>2</sup>, Frank M. Biro<sup>3,4</sup>, Larry H. Kushi<sup>5</sup>, Lusine Yaghjian<sup>1</sup>, Antonia Calafat<sup>6</sup>, Kayoko Kato<sup>6</sup>, Paul Succop<sup>1</sup>, M. Kathryn Brown<sup>1</sup>, Ann Hernick<sup>1</sup>, Robert Bornschein<sup>1</sup>

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**Background:** Polyfluoroalkyl compounds (PFCs) and their salts, such as perfluorooctanoic acid (PFOA), have been reported to change mammary gland structure and function in laboratory animals. We explored the relationship between serum PFOA concentration and pubertal maturation in young girls.

**Methods:** Within the NIH Breast Cancer and the Environment Research Centers (BCERC), we conducted a study of multiple environmental biomarkers, including PFOA and other PFCs in serum of young girls (age 6-7 years at entry) from two sites (N=689 girls). Pubertal staging (breast (B) and pubic hair (PH)) has been conducted by clinicians or trained research staff, every year or more frequently, for as long as four years. After calculating adjusted geometric means for all PFCs, we examined the relationship between PFOA serum concentration at the beginning of the study, with body mass index (BMI) and pubertal Stage 2 at baseline and one year follow-up.

**Results:** Detectable serum levels of five PFCs, including PFOA, were found in >95% of the girls. The PFOA median was 6.4 ng/ml (range <LOD 0.1 to 55.9 ng/ml), with 24.9% having values above the 95<sup>th</sup> percentile for children 12-19 years (NHANES 2003-2004 population (8.6 ng/ml)). At the follow-up visit, 28.3% of girls had reached Tanner stage B2+, 19.2% were PH2+ and 30.3% had a BMI percentile for age >85. In analyses where serum PFOA was modeled as a continuous variable, we found a direct relationship with pubertal breast status and an inverse relationship with BMI percentile at the follow-up visit, with adjustment for age, race, site and caregiver education.

**Conclusions:** It appears that PFOA acts as an endocrine disruptor although perhaps not by the usual mechanism. Although the relationship with BMI was inverse, there was a direct relationship with breast maturation. We continue to explore these complex relationships in models including other covariates.

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*The findings and conclusions in this presentation have not been formally disseminated by the Centers for Disease Control and Prevention and should not be construed to represent any agency determination or policy.*

## **Killing the Good Guys - How Selective Elimination of Normal Human Breast Cells by Radiation Can Promote Growth of Pre-Malignant Cells**

Paul Yaswen, *Lawrence Berkeley National Laboratory*

A current weakness in breast cancer risk assessment models is the lack of consideration of factors that influence the susceptibility of mixed cell populations to malignant transformation. Measurements of biological events in individual cells do not describe how an organism will respond to environmental stress. A major challenge is to understand how individual cellular responses are integrated in multicellular contexts resulting in health effects in humans. For example, while carcinogenic consequences of radiation exposure have historically been attributed to targeted effects – misrepaired DNA damage directly caused by dose-dependent ionization events, radiation can also induce “non-targeted” effects associated with malignant progression. In this study, we used an integrative biology approach to ask whether radiation – a well-studied cellular stressor, can promote the outgrowth of pre-malignant breast cells through selection of cells bearing particular epigenetic traits.

Our data indicate that through differential senescence-inducing effects, radiation can passively allow the outgrowth of pre-existing cells with aberrant self-renewal properties. These “variant” human mammary epithelial cells (vHMEC) lack inducibility of the tumor suppressor gene, p16. As others and we have observed, radiation itself does not appear to be a direct inducer of p16. However, our new results indicate that radiation-induced stress can be integrated with p16-inducing factors to cause premature growth arrest and senescence of normal cells. We used an agent-based model to evaluate the consequences of this process, and showed that it can allow vHMEC to overtake and fill the voids created by the prematurely senescing normal cells. The expansion of such populations in situ would be expected to expand the target size in which additional malignancy promoting aberrations can occur, especially since others and we have previously shown that these selected populations are particularly susceptible to genomic instability.

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## Session III – Relate BCERC Findings to Other Studies and the Literature

### Components of Individual Breast Cancer Risk: A Genetics Perspective

Michael N. Gould, McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, WI

The risk for breast cancer in individual women is governed by the interaction of heritable genetic polymorphisms, environmental factors, and systemic and cellular physiology. Genetic factors range from high penetrant genes such as BRCA1 to low penetrant alleles such as those being discovered by GWAS studies and comparative genomics. Due to the fact that the former have a very low population frequency and the latter have a high population frequency, most heritable risks in the population come from low penetrant alleles. We have developed rat models to identify and characterize low risk alleles. For example, the rat risk allele *Mcs5a* modulates risk in rats exposed to various carcinogenic agents shortly after sexual maturity. In a ~12,000 women case-control study the same allele was shown to modulate risk to breast cancer. Thus far most rat and human low penetrant risk alleles are located in non-coding DNA. In several cases they control local gene expression. In some alleles gene expression is modulated in the presence or absence of environmental stressors, while in others the regulatory activity of these risk alleles is only seen in the presence of environmental agents. Interestingly, some risk alleles function in the mammary gland while others function in other cell types such as in T-cell lymphocytes. Based on these studies of the interaction of risk genetics and xenobiotics, we are now in a position to add systemic and cellular physiology to our modeling. An important aspect of this model component is physiologic driven “windows” of breast cancer susceptibility.

### **Early Exposure to Endocrine Disruptors and Its Effect on the Breast: Evidence from Two Longitudinal Studies**

Brenda Eskenazi, *University of California Berkeley*

Growing evidence has indicated that endocrine disrupting chemicals introduced in early developmental stages may affect breast development and set the stage for breast cancer. The Center for Children's Environmental Health Research at UC Berkeley was established in 1998, and has examined the association between environmental contaminant exposure and precursors shown to be associated with breast cancer and breast cancer risk through two longitudinal studies. The CHAMACOS Study began in 2000, and is currently examining the association between DDT and PBDE exposure on age at pubertal onset in a longitudinal cohort of Mexican-American children in the Salinas Valley of California. Blood measurements were taken from the mothers during pregnancy, and the currently 9-year-old participants are being examined for pubertal tanner staging every 6 months until age 12. A number of studies have found an association between early age at pubertal onset and breast cancer.

The Seveso Women's Health Study (SWHS) is a retrospective cohort study of female residents of Seveso, Italy where a chemical explosion resulted in the highest levels of TCDD exposure experienced by a human population. Using data from the Seveso Women's Health Study, we examined the association between individual serum TCDD levels and reported age at menarche for women premenarcheal at the time of the explosion. Furthermore, data from this study was used to examine the association between TCDD level and breast cancer risk in women residing around Seveso, Italy, in 1976, at the time of the explosion. Results demonstrated a significant association between individual TCDD serum and breast cancer incidence, but none was found between TCDD level and age at onset of menarche.

These two studies, while different in population and exposure, examine the potential effects of endocrine disrupting chemicals on the breast.

### **Comments and Speculations about Endocrine Disruptors**

Melvin Grumbach, MD, *University of California San Francisco*

International studies suggest that the age at which children are entering puberty has fallen. The evidence suggests this is occurring in various ethnic groups, including internationally adopted children raised in new cultures. Most of these studies are retrospective or cross sectional. Some have speculated that endocrine disruptors may contribute to the advance in the age of puberty. Endocrine disruptors have been implicated in the increase in prevalence of the fall in the age of onset of puberty, for example, and its relation to breast cancer in later life and to the increased prevalence in some developed countries of testicular dysgenesis and testicular cancer. It has been suggested that intrauterine as well as perinatal exposure to endocrine disruptors is an important factor.

## **Session IV – Pathways from the Environment to Breast Cancer: The BCERC Transdisciplinary Model**

### **Pathway Models for Inter-Related BCERC Outcomes**

Paul A. Succop, Ph.D., *University of Cincinnati*

Pathway models, also known as structural equation models (SEM), are used to estimate the often complex relationships among correlated outcomes. SEMs usually involve mediator variables that operate between the predictors and the ultimate outcome of the causal chain. SEMs allow the estimation of both direct effects and indirect effects, which are the result of a distal variable operating through one or more mediators. Modern SEM software can simultaneously estimate linear and logistic regression equations, i.e., odds ratios and linear regression beta weights may be calculated in the same model. The application of a SEM to BCERC outcomes (breast development and BMI) will be discussed as an example of the SEM approach in this presentation. As sub-models of this particular SEM have been previously investigated, a comparison to the single outcome models will be performed.

## Hormones, Inflammation, and Diet

Richard C. Schwartz, Yong Zhao, Ying S. Tan, Weizhong Wang, L. Karl Olson, and Sandra Z. Haslam, *Departments of Microbiology & Molecular Genetics and Physiology, Michigan State University, East Lansing, MI 48824*

Progesterone (P) promotes cell proliferation and development of the normal mammary gland, and is implicated in the etiology of breast cancer. We recently showed that P induces inflammation in the mammary epithelium. The role of hormones, particularly P, in mediating inflammatory processes in the mammary gland was not previously recognized. We found progestin treatment of cultured mammary epithelial cells to induce production of several proinflammatory gene products. These products increase expression of proinflammatory cytokines in monocytes, and promote monocyte recruitment and adhesion. Inflammatory processes are required for tissue remodeling and angiogenesis, essential for normal mammary gland development. In the context of mammary carcinogenesis, these same processes can promote tumor development. Long-term P exposure alone or in combination with estrogen (E) promotes development of mammary cancer in rodents, and in humans, as evidenced by increased breast cancer risk in postmenopausal women receiving hormonal therapy with combined E plus progestin, but not with E alone. Further, the recent significant decrease in breast cancer incidence is credited to decreased postmenopausal hormonal therapy. The ability of P to mediate mammary gland inflammation presents a plausible mechanism underlying the promotional effects of P in mammary tumorigenesis.

*In vivo* analysis of P's inflammatory effects in mammary glands of BALB/c and C57BL/6 mice shows that P induces a broader range of proinflammatory cytokines/chemokines in BALB/c mammary glands than in cell culture. In contrast, C57BL/6 mice show less robust induction of proinflammatory factors. In BALB/c mammary glands, P treatment induces Ccl20, Cxcl5, Defb1, IL-17B, RANKL, SAA1, and TNF $\alpha$ . RANKL induction is particularly robust: 275-fold. While Defb1 is strongly induced in C57BL/6 mammary glands, Cxcl5 and RANKL are more weakly induced, and Ccl20, IL-17B, SAA1 and TNF $\alpha$  are not significantly induced. The weaker inflammatory response of C57BL/6 mice to P is consistent with our previous findings that adult C57BL/6 mice show reduced proliferative and morphological responses to P. One common property of RANKL, IL-17B, and TNF $\alpha$  is their ability to induce activation of NF- $\kappa$ B, a critical proinflammatory transcription factor. The broader range of cytokines/chemokines observed in the whole gland versus cultured epithelial cells suggests participation of both epithelial and stromal elements in their expression. Our findings suggest a chain of events where P induces RANKL, an activator of NF- $\kappa$ B, which in turn induces other proinflammatory cytokines and chemokines that recruit macrophages to the peri-epithelial stroma. We confirmed that both macrophages and eosinophils are among the leukocytes recruited on P treatment, and that RANKL can induce SAA in cultured BALB/c virgin mammary epithelial cells and in a mammary epithelial cell line.

We recently found that a high fat diet (HFD) stimulates both mammary gland development and DMBA tumorigenesis in BALB/c mice, while inhibiting mammary development in C57BL/6 mice. HFD also stimulates RANKL expression in the mammary glands of BALB/c mice, suggesting that HFD induces inflammatory effects similar to those observed in P treatment. In C57BL/6 mice, we found that HFD and associated increased adiposity elevates serum leptin. Elevated leptin is generally associated with increased inflammation that might be expected to enhance development. However, lymphocytes from obese C57BL/6 mice are known to produce elevated levels of IL-4, which is known to suppress RANKL signaling and may suppress P-induced inflammation in the mammary gland. Further studies are warranted to determine how inflammatory processes in the mammary gland may be modulated by environmental exposures, such as diet, which may be relevant to human breast cancer.

This work is supported by the Breast Cancer and the Environment Research Center: NIH/NIEHS/NCI U01 ES12800.

### **Pathways from the Social Environment through Psychological Factors and Biology**

Robert A. Hiatt, Julianna Deardorff, Carolyn Fang, Suzanne Miller, Dejana Braithwaite, David Rehkopf, Irene H. Yen, and Maida Galvez

Socioeconomic status (SES) is known to be directly related to risk of breast cancer in adult women. The most common explanation for this observation suggests the influence of reproductive factors such as earlier age at first birth, higher parity, later age at menopause and earlier age at menarche. However, these reproductive variables do not fully explain breast cancer risk and the public and many scientists are concerned that environmental exposures may be at play. The search for chemical and physical environmental factors that influence breast cancer has been primarily in adult women. However, there is now much evidence that exposures and experiences during early development in girls may be critical in understanding the etiology of breast cancer. In the epidemiologic studies within the BCERC network we have gathered information on SES, race and ethnicity, the built environment, and family and psychological factors as well as lifestyle behaviors, such as dietary patterns and physical activity, and the physical (chemical and radiation) environment. To increase our understanding of the inter-relationships of these factors we have taken a transdisciplinary approach drawing on social epidemiology, developmental psychology, geography and medicine.

We will present the evidence for the association of SES as indicators of social disadvantage with the onset of puberty as measured by Tanner breast stage 2. We will then discuss three possible pathways from low SES to earlier age of pubertal onset in the BCERC cohort. These are: 1) the influence of familial and individual factors such as adverse family dynamics, parental psychopathology and family composition (e.g., absent biologic fathers) 2) material deprivation, and 3) lifestyle factors such as obesogenic diets and lower levels of physical activity. The presentation will draw on evidence gathered from BCERC studies thus far as well as from the extant literature.

## Session V: Translation and Dissemination

### **The Role of High Credibility Message Sources and Personal Language in Communicating Breast Cancer Risk to Advocates and Mothers**

Charles Atkin, Michigan State University

Breast cancer messages focused on early adoption of healthy behaviors provide a fruitful avenue to potentially decrease the number of females who will be diagnosed with breast cancer later in life. The current study used a 2 (message source) x 2 (personal language) x 3 (message concept) design to expose women (N=590) to one of three message concepts (e.g., understanding normal mammary gland development, limiting exposure to chemicals, & adoption of healthy lifestyle behaviors) with a physician or a researcher as the message source, and personal or impersonal language used in the messages. After reading one experimental message, women completed a post-test survey designed to assess message and source perceptions, knowledge of the message content, attitude, efficacy, behavioral intentions, and demographic information. Results indicated that both message sources were perceived as highly credible, and that the personal level of language did not impact attitude or intentions. Women who were advocates differed from other participants in their perceptions of source credibility across messages. Additionally, lower behavioral intentions were associated with the mammary gland development message. Implications of the results for future breast cancer message design will be discussed.

### Pediatricians as Key Targets for Knowledge Dissemination and Integration

Julie Harris, PhD, MPH, *University of California San Francisco*

There is a growing concern among practitioners, policymakers, legislators, and the public over the translation of research into practice. The Institute of Medicine (IOM) has concluded that in many areas of public health and clinical practice, we need to recommend strategies based on the best available evidence as opposed to waiting for the best possible evidence. The CYGNET project and the other BCERC sites have generated research findings, which need to be disseminated to the broader public. Furthermore, pediatricians who are the main trusted voice for parents on matters of children's health, often lack adequate training in risk assessment, and environmental health sciences.

In order to address the need for dissemination and to connect the message with the messenger, we have developed a novel dissemination strategy with pediatricians as our key target. The goal of the dissemination plan is to educate pediatricians on three topics: basic risk factors for early pubertal development, current trends and cultural/ethnic differences in bay area girls' pubertal development (a topic of some clinical importance), and current geographic differences in levels of key endocrine disruptors that may influence pubertal development. The main goal of this dissemination plan is to increase knowledge for improved clinical decision-making and to assist pediatricians' in discussing this information with their patients.

Dissemination science is a growing field and we still know very little about how to best disseminate emerging research findings. Thus we are devising an evaluation plan to determine the reach, effectiveness, adoption, and uptake of this particular dissemination strategy. **This study has two main objectives.** The first is to develop and implement a videoconference and accessory strategies to disseminate evidence to pediatricians. The second is to evaluate whether and how this videoconference influenced pediatricians' knowledge, communication with patients, and their ability to integrate this information into their clinical practice.

We are currently designing the videoconference in collaboration with Kaiser Permanente's continuing medical education department. We will hold the videoconference in spring, 2010 with nearly 600 Kaiser Permanente pediatricians. Additional reinforcing resources and tools (e.g. lay monograph, brief research fact sheets) will also be disseminated to pediatricians in early spring, 2010 as part of the dissemination plan. We are employing a pre-test, post-test design to evaluate the effectiveness of the dissemination strategy among participating northern California pediatricians. Participants will complete a self-administered web-based survey prior to participation, immediately following participation, and three months later. The main outcomes being assessed on the survey will be: knowledge, communication with patients, intention to integrate information into patient risk assessment and counseling, and referral practices.

Currently there is no empirical evidence regarding how to effectively disseminate research findings to pediatricians, or what the minimal level of dissemination intensity necessary to produce a meaningful change in clinical practice. This study will provide evidence on both of these points in order to advance our understanding of effective evidence-based dissemination strategies going forward.

## Communicating Individual Level Biomarker Data to Participant Families: Findings from the CYGNET Study

Gayle C. Windham, PhD, *Environmental Health Investigations Branch, California Department of Public Health, Richmond, CA*

**Background:** CYGNET is one of the studies being conducted within BCERC to investigate factors related to pubertal development in girls. Urine and serum biospecimens were collected from the 440 girls for measurement of numerous chemical metabolites within several families, including phenols, phytoestrogens, phthalates, PCBs, organo-chlorine pesticides, brominated fire retardants, and per-fluorinated compounds, in addition to annual exams and caregiver interviews. The biomarkers were measured for research purposes because of suspected hormonal activity, but little is known about their actual health effects or “safe” levels. Although individual results were not promised to families, the researchers and COTC feel there are ethical imperatives for providing them. Numerous considerations arise in communicating this magnitude of technical information that does not have clear clinical ramifications.

**Objectives:** To inform the process of reporting the biomarker data, we conducted focus groups with caregivers. The objectives were to gauge the level of interest in receiving individual results, determine the preferences for format and content of report-back materials as well as the method for providing results, and gather other information that would add to our understanding of how to appropriately provide results, including participants’ experiences during the study, their understanding, misconceptions or fears about environmental exposures and health, and how they might use the girls' results.

**Methods:** Four focus groups were planned, of 8-12 participants each, randomly recruited from the entire cohort, with one for Spanish-speakers. Participants answered a few questions about demographics and literacy and then participated in a group discussion led by experienced facilitators following a script and using examples of report-back materials derived from other studies.

**Results:** Of the 35 attendees, all but one was parent of a girl in CYGNET, and the majority (89%) were female. Compared to the entire cohort, focus group participants were more likely to be Hispanic (40%) and less likely to be Asian (only 1), and were somewhat less educated. The mean age was 45y, with a range of 30 – 73y, and some variation by ethnic group. Participants over-whelmingly wanted to receive their daughters’ results, but were divided about whether the girls should receive them at the same time. Other dominant themes included wanting to know how their daughter’s levels compared to other CYGNET girls, as well as other cohorts, and being provided thorough information on what is known about the chemicals, including ways to limit exposure. Examples of the report-back materials will be presented, as well as other results.

### **Increasing the Social Impact of Cancer Information**

Matthew W. Kreuter, PhD, MPH, *Washington University St. Louis*

To help eliminate breast cancer disparities, it is essential to increase the reach and effectiveness of health information to women most affected by the disease. This presentation will describe four communication-based projects to eliminate breast cancer disparities in African American women. In the first we evaluated use of computerized interactive breast cancer information kiosks placed in beauty salons, churches, neighborhood health centers, social service agencies, public libraries and Laundromats. In the second, we established a news service that creates community specific cancer news releases for African American newspapers, and tested its effects in 24 U.S. cities. Third, we have compared the effects of breast cancer information delivered through survivor stories to traditional forms of cancer communication. Finally, we have partnered with StoryCorps, the national oral history project, to capture cancer stories from patients and their families for use in interventions to help parents talk to their children about cancer. This collection of successful projects illustrates key principles and processes that can be applied to a range of breast cancer communication challenges in diverse populations and settings.

## Framing Science: Communicating Biomedical Results to Nonscientific Audiences

Bradford W. Hesse, PhD, *National Cancer Institute*

Communicating scientific data to the public, especially in an age of sound bite journalism, can be a point of frustration and concern for many health researchers. For example, preliminary findings from exploratory studies may be unexpectedly framed by the popular media as being more conclusive than the data would support; while presentations of reliably strong findings – such as the link between tobacco exposure and lung cancer – may be called into question by industry spokespersons peddling “doubt” as a way of muddying the debate and protecting self-interest. In this context, it may be tempting for many health scientists to withdraw from public discussion. Yet, without the active participation of content experts, the public often finds its understanding clouded by disconnected reports of data, a problem of the information age that journalist David Shenk referred to as “Data Smog.” To empower scientists with tools for cutting through that smog, this talk will summarize some of the key psychological findings on how to communicate data to lay audiences effectively. Using an “OPT In” framework, the talk will illustrate how *Organization, Planning, Testing*, and keeping an eye toward *Integration* can help place the public conversation back onto a foundation of evidence. Organizing refers to identifying findings that are ready for dissemination, evaluating levels of evidence (from settled vs. controversial science), and thinking through issues of timing and public need. Planning phase refers to the preparations customarily undertaken through any major communication activity including: (a) identifying objectives, (b) analyzing audience(s), (c) considering context / medium, (d) developing preliminary messages, and (e) creating a plan for reaching audiences. Testing refers to the formative evaluation processes that can be used to improve the fidelity, usability, and utility of the message and accompanying materials. Testing methodologies may range from the use of qualitative techniques such as focus groups and concurrent protocol analysis to quantitative analyses of Web traffic, survey data, or objective quality indicators. Integrating recognizes that the biggest problem for most consumers is figuring out how new data may relate to old, and what the implications would be for their own healthy behaviors. In health communication, “problem” messages that are not connected to explicit safety messages can lead to paralysis, fear, inaction, and /or blunting. Opting in to the conversation means going through all the steps of connecting a cogent message to targeted audiences in usable ways.

## Session VI: Public Health and Policy Implications

### California's Green Chemistry Initiative

Jared Huffman, *California State Assembly, 6th District*

For years, consumers have been exposed to chemicals in commonly used products that are now known to be carcinogenic and/ or bad for our health. The State of California plays an important role in protecting the public from materials known to cause cancer, reproductive problems, and other deficiencies and disorders that have a negative impact on public health and the environment.

The California Legislature has passed laws to govern the use of some chemicals including mercury, lead and phthalates during the past two decades, and a significant advance in chemical policy occurred in 2008 when the Governor signed AB 1879, legislation jointly authored Assemblymembers Mike Feuer and Jared Huffman . Arguably the most important toxics legislation in many years, this bill creates broad authority for the Department of Toxic Substances Control (DTSC) to regulate hazardous chemicals in consumer products and provides an array of enforcement tools.

Under the bill, DTSC is charged with responsibility for establishing regulations and implementing the law by January of 2011. DTSC has already released draft regulations, referred to as a straw proposal, which include recommendations from a Green Ribbon Science Panel, and public hearings are being conducted to solicit stakeholder feedback. While there is room for improvements in this straw proposal, it captures the essence of AB 1879 in seeking to regulate thousands of hazardous chemicals of concern and pressure manufacturers to design safer products.

AB 1879—Green Chemistry—will fundamentally transform how chemicals are managed in order to better protect our workers, children, public health, environment, and the economy. For the first time, our state's scientists and regulators will have the authority and the information necessary to establish the state's first comprehensive Green Chemistry Program—a science-based approach to identify and prioritize chemicals of concern, determine how best to limit exposure or reduce the level of hazard posed by toxic ingredients, and regulate consumer products. The Green Chemistry Program in California is an important step towards creating a cleaner, safer, greener California.

## Science for Effective Public Policy: Through the Lens of the Breast Cancer and Chemicals Policy Project

Megan R. Schwarzman, MD, MPH, *Program in Green Chemistry and Chemicals Policy, Center for Occupational and Environmental Health (COEH), School of Public Health, University of California, Berkeley*

Environmental health scientists can advance public health by translating research to inform effective implementation of science in decision-making. This session will explore these links through the lens of the Breast Cancer and Chemicals Policy project. This year-long project aims to: 1) Identify key toxicological methods for detecting chemical contributors to breast cancer, 2) Investigate testing strategies that will provide the most useful information to policy makers, consumers and businesses attempting to reduce chemical hazards, and 3) Recommend means for addressing current gaps in toxicological methods and scientific knowledge in order to more effectively manage chemicals.

## The Health Care Delivery System in the United States: Failure in Translation

Kenneth Olden, PhD, ScD, *Founding Dean of the Proposed School of Public Health at the City University of New York*

Residents in socioeconomically disadvantaged communities surrounding some of the best medical centers in the world, are dying from preventable or curable diseases. In fact, the US government acknowledged that disparities in mortality, from causes attributable to modifiable risk factors, were a reality for many Americans with the publication of the Heckler report in 1985. Since the publication of this seminal report, the elimination of health disparities has been touted as a priority of the US Department of Health and Human Services. We and others have argued that of the various known contributors to health disparities upstream social and environmental factors are the ones that are most amenable to intervention through public policies. Recently, policy makers have focused on the disproportionate exposure to environmental hazards and reduced access to health care. In this presentation, I will discuss the health care delivery system from the point of view that it has failed to ensure good health for millions of Americans in spite of the nation's enormous investment and leadership in research, training and technology development. Finally, I will make the case that the evolving health care reform legislation does little to address affordability and other inherent limitations of the current individualized or physician/patient health care delivery model.