



Special Research Initiatives (SRI)

Initiative Summaries
and Funded Projects

AUGUST 2012

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Background

In 2004, the CBCRP Research Council (Council) completed a comprehensive review of the program and decided to allocate 30% of the funding between 2004 and 2009 to a Special Research Initiatives (SRI) to support research that addressed:

1. The effects of the environment on the development of breast cancer; and
2. Disparities in breast cancer, i.e., the reasons why some groups of women are more likely to get breast cancer or to die from the disease.

The SRI was designed to fund research that not only increased knowledge about these topics, but also pointed to solutions that would reduce the suffering from breast cancer and move science closer to eliminating the disease.

A multi-year strategy development process was launched to leverage California's unique and diverse geography, population and research resources, and to avoid duplicating previous research. The five-part SRI strategy development began with the recruitment of the Steering Committee—a group of national experts and advocates to lead the effort.

The 2nd step involved an extensive review of the literature on the role of the environment in breast cancer and disparities in the disease. More than 50 writers and scientific advisors from various fields were engaged to produce a 500+ page report,

“Identifying Gaps in Breast Cancer Research”. Science advisors also offered recommendations for research in their topic areas.

Stakeholders from affected communities, funding agencies, governmental bodies, academia, clinical fields and advocacy organizations were engaged in brainstorming ideas for research in step 3. More than 200 people attended meetings across California and teleconferences, generating hundreds of ideas. These were synthesized and stakeholders sorted and rated the final 95 ideas on potential impact, uniqueness and feasibility.

For the 4th step, a 40-person Strategy Team was formed. Using the Gaps document, a database of 191 California resources and research ideas that they helped generate, the Strategy Team worked together over six months to identify and prioritize innovative strategies. They worked in teams with CBCRP staff to develop 10 Concept Proposals with detailed research questions and approaches. The Concept Proposals were assessed by the Steering Committee.

In 2008, the Steering Committee took the final step, presenting possible research packages to the Council for their consideration. In conjunction with Steering Committee members, the Council arrived at and adopted a SRI funding strategy. Since that time, CBCRP staff has implemented the strategy, with the oversight of the Council

and periodic input from former Steering Committee and Strategy Team members. In 2011, the final SRI research projects were funded.

In March 2010, the council decided to build on the existing SRI by devoting 50 percent of CBCRP research funds for the next five years. The focus was expanded to include:

1. Population-level interventions (including policy research) on known and suspected risk factors and protective measures; and
2. Targeted interventions for high-risk individuals including new methods for identifying or assessing risk.

This document provides basic information on the projects funded in the SRI to inform thinking about future research recommendations. The Initiatives are organized by topic: Disparities, Environment and both, followed by a description of efforts to facilitate collaboration between grantees.

For each Initiative, the following is included:

- RFP or RFQ Goal (goal from the concept paper used in the Request for Proposal or Request for Qualifications)
- Application Process Results (number of applications received, etc.)
- Funded Research including:
 - Title
 - Award Period
 - Principal Investigator(s)
 - Research Aims
 - Methods
 - Progress (abstracts from any reports to date)

DISPARITIES

1. Understanding Racial and Ethnic Differences in Stage-Specific Breast Cancer Survival

RFQ Goals: Feasibility Study

To determine the feasibility of combining data from case control and cohort studies in California. The feasibility study will focus on the comparability of survey instruments and databases, quality and type of additional data which could be linked to data from study participants, and the specific research questions that can only be answered by pooling data from these studies. Additionally, IRB and individual study approvals to share data will be sought during the feasibility phase.

Specific research questions can be developed by the PIs after a full assessment has been done of the data that can be pooled from the studies as well as other data that can be linked to the data from the study participants.

RFQ Goals: Full Study

1. To explore the interaction of factors (tumor, individual, social, environmental, genetic) which account for racial and ethnic differences in stage-specific survival among women diagnosed with breast cancer in California.
2. To examine whether these factors lead to higher risks in certain racial and ethnic groups than in other groups (interaction effects.) To identify specific areas for intervention or for further, more detailed investigation.

Application Process Results

CBCRP invited representatives of the breast cancer studies that had been identified in the SRI development process to apply and sent the announcement out widely to others involved in breast cancer research. No new studies were identified and all invited researchers applied and participated in the pilot. Only those involved in the pilot were eligible for the full award Consortium.

Pilot Study Results

This project brought together collaborating researchers from five research institutions representing seven breast cancer studies for a pilot project to determine the feasibility of pooling data and identify important research questions. Details about the pilot awards are available on the CBCRP website in the Research Portfolio. Based upon that work, this group successfully proposed a 3-year study and the formation of a consortium to address four research questions. One of the requirements of these awards is to collaborate with grantees funded under other initiatives. Details of their collaboration to date are in the last section of this report.

Funded Research

TITLE	California Breast Cancer Survivorship Consortium
AWARD PERIOD	1/1/2011 – 12/31/2013
COLLABORATORS	<ul style="list-style-type: none"> • Anna Wu, PhD, University of Southern California and the Breast Cancer in Asian-American Women Study (Facilitator) • Leslie Bernstein, PhD, Beckman Research Institute of the City of Hope, Women’s CARE Study and In Situ Breast Cancer Study, California Teachers Study • Scarlett Gomez, PhD, Northern California Cancer Center, SF Bay Area Breast Cancer Study • Marilyn Kwan, PhD, Kaiser Foundation Research Institute, Life after Cancer Epidemiology Study (LACE); Pathways (withdrawn) • Kristine Monroe, PhD, University of Southern California, Multi-Ethnic Cohort
RESEARCH QUESTIONS	<p>The overall aim was to examine four groups of exposures: contextual factors, physical activity, body size, and comorbidities, and determine whether separately or in combination they explain the differences in stage-specific breast cancer survival by race and ethnicity. These four primary exposures were selected because of their modifiable nature, their documented variability across racial/ethnic groups, their associations with breast cancer mortality in general, their potential for broad impact in reducing disparities in breast cancer survival, and their consistent collection and availability across the studies.</p>
METHODS	<p>Collaborating partners created the California Breast Cancer Survivorship Consortium (CBCSC), consisting of seven California-based breast cancer studies with over 16,000 breast cancer cases, including 2603 African Americans, 2113 Asian Americans, 2582 Latinas, and 9306 non-Latina Whites. Consortium members pool study data into two Core data sets and pursue analyses associated with modifiable factors associated with racial/ethnic differences in stage-specific breast cancer survival. These interrelated factors are to be investigated among these racially and ethnically diverse breast cancer survivors in four Projects.</p> <p><i>Project 1: Contextual-level factors</i></p> <p>The impact of contextual-level socioeconomic status (SES) and the interaction with individual-level education on survival;</p> <ul style="list-style-type: none"> • The impact of the built environment (neighborhood attributes that promote walking and healthy living, such as availability of parks, healthy eating places, mixed land use) and the interaction with individual-level BMI and physical activity on survival; • The impact of ethnic enclaves and the interaction with individual-level migration characteristics (nativity, age at migration, language usage) on survival; and • The impact of institutional (hospital-level) factors such as ownership status, academic affiliation, patient composition (SES and race/ethnicity), distance to medical facilities with individual-level education on survival.

Project 2: Physical activity

Determine whether recreational, occupational and total (recreational and non-recreational) pre-diagnosis physical activity are independently associated with death due to breast cancer and death due to any cause.

Project 3: Body size

Examine the associations between body size measures (body mass index, waist and hip circumference and waist-to-hip ratio around the time of diagnosis; and weight gain since age 18 or 20 years until time of diagnosis) and all-cause and breast cancer mortality by race/ethnicity, stage, tumor receptor status, and overall, adjusting for prognostic and lifestyle factors.

Project 4: Comorbidities

Determine the race/ethnic specific relationship between pre-diagnostic hypertension, diabetes, heart disease and the number of comorbid conditions and risk of overall mortality and breast cancer-specific mortality.

These factors were selected because they have been implicated to influence breast cancer mortality and the number of women with varying profiles of these factors differs by race/ethnicity. The Consortium will conduct generalizability analyses to assess the representativeness of the pooled study sample to the population-based cancer registry data.

PROGRESS: 2011

Study investigators, advisors and advocates hold semi-annual in-person meetings to discuss the objectives, deliverables, and time table for the study. They also have monthly conference calls to discuss progress and any concerns or issues. The activities they completed during Year 1 included: 1) established study website; 2) signed data transfer agreements between the participating institutions, 3) compiled cancer registry data for the cases from the six studies in Core 1; 4) checked poolability of data in Core 2 and Projects and harmonized variables; 5) completed data exchanges for the two Cores and 4 Projects, 6) developed preliminary statistical model, and 7) completed preliminary analyses using summary variables in Cores 1 and 2 and in each of the four Projects.

Over the reporting period, they encountered a few challenges. First, the Principal Investigator for one of the original studies decided not to participate. This decreased the overall sample size, but most of that study's participants were recently diagnosed and had limited follow-up time, so this will not substantially affect the statistical power of the pooled analyses. Another challenge was in learning that protected health information (PHI) for the LACE participants could not be released. PHI is needed to link the LACE participants to their cancer registry record and to enable the contextual analyses. The Collaborators worked with the Kaiser collaborators to request a HIPAA waiver from the Kaiser IRB, which was granted.

Project 1: Contextual-level factors

Conducted preliminary analyses examining individual-level education and block-group level socioeconomic status

Project 2: Physical activity

Created recreational physical activity variables for the three participating studies: average hours per week each year and average metabolic equivalent task (MET)-hours per week each year for long-term recreational physical activity (ages 10 through age at breast cancer diagnosis), recreational physical activity between ages 10 and 19 years, and recreational physical activity during 10 years before the woman's breast cancer diagnosis. The studies vary in several ways: with 13% to 21% and 26% of women inactive. Among physically active women exercise ranged from 1.8 to 2.6 and 2.9 hrs/wk/yr.

Project 3: Body size

Body size variables (pre- and post-diagnosis BMI, BMI at age 18 or age 20, and pre- and post-diagnosis waist-hip-ratio) were constructed for the 10,215 breast cancer cases included in this project. Preliminary survival models were run, and some potentially interesting results regarding the association of waist-hip-ratio and survival arose.

Project 4: Comorbidities

Preliminary analyses were conducted of pre-diagnostic hypertension, diabetes, and heart disease.

As of summer 2012, the collaborators have drafted a methods paper and submitted abstracts for presentations of preliminary findings.

2. Demographic Questions for California Breast Cancer Research

RFQ Goals

The aim of this project is to develop recommendations for researchers in gathering demographic information when conducting research on breast cancer in California. The demographic domains of interest include: race, ethnicity, community characteristics, migration history, disability status, socio-economic status, gender, and sexual orientation. Each of these domains of interest is infused with cultural beliefs emanating from shared experiences and generational transference which can influence behavioral and lifestyle factors that likely impact risk, screening and treatment decisions and access, utilization, and survival rates.

Application Process Results

CBCRP received three applications in response to the Request for Qualifications. The reviewers gave all of the applicants high scores, but only one project could be funded.

Funded Research

TITLE	Demographic Questions for California Breast Cancer Research
AWARD PERIOD	3/1/2009 – 2/29/2012
PRINCIPAL INVESTIGATOR	Scarlet Lin Gomez, PhD, Northern California Cancer Center
RESEARCH QUESTIONS	This project proposed to identify demographic measures that would improve understanding of disparities in breast cancer.
METHODS	Researchers at the Northern California Cancer Center and their collaborator at Harvard University, Nancy Krieger, worked closely with scientific and community experts to develop a set of survey tools that will be used to gather data associated with breast cancer disparities more consistently. The standards for data collection that are developed through this study will help to ensure that scientists can effectively interpret and compare information they use to study breast cancer. Factors to be surveyed included an individual's race, ethnicity, birthplace, migration history, language, community characteristics, disability status, socioeconomic status, gender, and sexual orientation. Additionally, the survey tool used in this study were to be translated into several major languages and reviewed and tested by a wide range of experts, making it applicable to gathering data for research within many different populations.

**PROGRESS:
2010**

During the first year of the study, the researchers conducted, documented, and synthesized a comprehensive review of existing survey instruments. They convened a one-day meeting of 11 expert advisors and a half-day meeting of 10 community advisors. They developed telephone and self-administered versions of a survey instrument to be tested via cognitive (think-aloud) and pilot interviews. This instrument was approved by the institution's and the state's IRBs, and was in the process of being translated.

**PROGRESS:
2011**

The researchers translated the survey instrument into five languages, hired and trained bilingual interviewers, and began cognitive testing for comprehension and cultural appropriateness. The IRB approvals included a contingency for making minor revisions during the cognitive testing process, so that questions testing as problematic could be adjusted.

In the past year, the researchers conducted cognitive interviews in 6 languages, devised a systematic method for analyzing results, consulted with scientific advisors regarding issues, and refined survey questions as necessary. While their original survey tool was drafted in consideration of an 8th grade reading level, cognitive testing revealed that adjustments were necessary to further reduce reading and comprehension levels, and some questions were dropped. After these changes, they did a second round of cognitive testing. Concurrently, the researchers are developing a detailed "Q x Q" (including source and origins of questions, how and why they were modified, recommendations for their use, and reasons why certain questions were dropped).

Due to the extent of the changes to the survey instrument, subsequent retesting, and the resignation of the Tagalog interviewer (and difficulty hiring for this position) the researchers requested and were granted a no cost extension to finish their work.

Another CBCRP project adapted this survey instrument for on-line self-administration and provided feedback to the researchers in May 2012.

FINAL

Despite experiencing barriers related to staff attrition, IRB delays, and unexpectedly low study response rates, this team successfully completed the originally proposed activities and assembled several resource documents that researchers can utilize in considering using these survey items in their research.

Although they employed a multi-method, mixed-method approach to developing and testing these sociodemographic survey items, they were not able to test items as thoroughly as they wanted. The expectation is that these survey items will continue to be refined through use by these and other researchers. They will make these materials available through a website, and to encourage their use and further testing by sharing them through word of mouth with colleagues.

3. Piloting an Integrated Approach to Understanding Behavioral, Social and Physical Environment Factors and Breast Cancer among Immigrants

RFP Goals

For a given immigrant population, researchers should gather and/or pool and analyze multi-level data to provide a more richly detailed description of what environmental, social and cultural factors associated with immigration (e.g. rates of acculturation), influence breast cancer risk. Successful applicants will address one or more of the following:

- A. Which structural, social and physical environment and occupational factors (e.g. neighborhood characteristics, employment networks) most affect breast cancer risk and/or outcomes among immigrants? Why and/or how do they occur?
- B. How does the timing of immigration (stage of life) and the associated changes in behavior and exposure effect breast cancer risk? (Incidence? Outcome?) How does this differ with varying rates of acculturation?

- C. What intergenerational differences exist in exposures, risks and outcomes and how are they determined?
- D. What differences can be biologically measured among first and second generation immigrant women, pregnant and otherwise, that might influence breast cancer risk?

Application Process Results

In response to the Request for Proposals, CBCRP received seven applications. One grant was awarded, which used less than half of the funds allocated for this Initiative. The other proposals were found to lack scientific merit. Common reviewer concerns included objectives being too broad, use of multi-level factors that were not well integrated; not accounting for the dynamic nature of immigration and/or the complexity of other data; and insufficient community involvement.

Funded Research

TITLE	The Immigrant Experience and Breast Cancer Risk in Asians
AWARD PERIOD	11/1/2011 – 10/31/2013
PRINCIPAL INVESTIGATOR	Scarlet Lin Gomez, PhD, Cancer Prevention Institute of California (CPIC)
RESEARCH QUESTIONS	This project proposed to 1) document the extent to which new and established risk factors among Asian Americans (AA) vary across over the lifespan and are affected by family and community influences; 2) explore new hypotheses relating to the impact of immigrant exposures across the lifespan on breast cancer risk, and 3) compile pilot data on effective strategies for recruiting AAs for future studies.

METHODS

The study proposed to examine the critical windows of exposure for risk factors like diet and weight gain, and for identifying new risk factors, including infectious exposures, family and community influences, and social stressors related to the process of immigration, being an immigrant, and to discrimination. This study will efficiently leverage CPIC's ongoing work with AA breast cancer cases being recruited through the population-based regional cancer registry as part of a currently funded cancer survivorship study called Equality in Breast Cancer Care (EBCC).

Some exposure data was to be obtained through the EBCC telephone interviews; a second interview would collect the additional information needed for the currently proposed study. The researchers proposed to incorporate existing data on community-level measures from their California Neighborhoods Data System, to relate community factors to individual-level risk factors and breast cancer risk. Controls were to be recruited using one of four methods: 1) an approach based on address directories; 2) the California Cancer Detection Program; 3) the Army of Women; and 4) various community-based approaches. The researchers expected these methods to be considerably more efficient than prior approaches in recruiting AA controls, and pooled together, were expected to result in a representative sample.

Within the first two months the grantees found that two of the original sources of controls were no longer feasible for recruitment into the EBCC study. The PI will continue to explore the effectiveness of recruiting through the Army of Women, although those participants are no longer eligible for enrollment into a study with follow on measures. Another online mechanism, Craigslist, will also be used. The other unavailable source is the state Cancer Detection Program. Instead controls will be recruited through Asian Health Services and other SF Bay Area community health clinics, which serve low-income Asians.

ENVIRONMENT

4. Toward the Development of a California Chemicals Policy that Considers Breast Cancer

RFQ Goals

The aim of this project is to use the current scientific knowledge base to develop timely recommendations for chemicals policy in California that will fill the data gap by considering the unique causal pathways thought to contribute to breast cancer. While another proposal will fund laboratory research to identify, evaluate, and develop new tests (see Proposal 7), this proposal focuses on the need to use what knowledge we have today to inform policy today. Specific questions to be answered include:

1. What data do consumers, businesses and government need to evaluate chemicals for their potential to contribute to breast cancer?
2. What causal and mechanistic pathways (mammary gland carcinogenesis, endocrine

disruption, developmental susceptibility, etc.) should be included when considering potential to contribute to breast cancer?

3. How can such data requirements be structured as a stepwise set of tests that can initially screen large numbers of chemicals and enable selection of potential contributors to breast cancer for further, more detailed tests?
4. What are the appropriate criteria for prioritizing potential contributors to breast cancer for testing and for biomonitoring?

Application Process Results

Despite extensive outreach, a single application was submitted. Fortunately, it was very strong and received solid scientific review scores.

Funded Research

TITLE	Breast Cancer and Chemicals Policy (BCCP)
AWARD PERIOD	1/5/2009 – 6/4/2013 (Supplemental extension awarded)
PRINCIPAL INVESTIGATOR	Megan Schwarzman, MD, MPH, University of California Berkeley and the Northern California Center for Occupational and Environmental Health
CO-INVESTIGATOR	Sarah Janssen, MD, PhD, MPH, National Resources Defense Council
RESEARCH QUESTIONS	<ul style="list-style-type: none">• Develop an approach for identifying chemicals that may contribute to the development or progression of breast cancer;• Identify research needs and recommend improvements to existing test methods; and• Pilot a model process that can be applied to other disease endpoints, enabling the ultimate aim of producing a comprehensive approach for identifying hazardous chemicals.

METHODS

The project sought to assess both existing toxicological tests and gaps in the availability of testing measures that could be used to prioritize which chemicals are of most concern for their links to breast cancer. A multidisciplinary panel of experts was to be convened to evaluate the existing scientific literature on causal pathways and suspected chemicals implicated in breast cancer and to identify significant gaps in current knowledge.

The panel was to summarize the causal pathways and outline a strategy for identifying chemicals suspected in the development of breast cancer and how toxicity testing methods could be used by California to pursue more effective management of chemicals. They were to recommend how to narrow the gaps in chemicals data, testing methods and scientific knowledge about the likely contribution of chemicals to breast cancer, and intended to propose a plan for disseminating their findings to policy makers, the breast cancer advocacy community, and scientists.

PROGRESS: 2010

Working from current epidemiologic and laboratory evidence, the Panel first identified changes in biological processes associated with the development or progression of breast cancer. Second, they identified existing toxicity testing methods that detect these changes. Third, the Panel designed a testing scheme, calling it the Hazard Identification Approach, for identifying chemicals that may raise the risk of breast cancer. The Panel also recommended methods for prioritizing the types of chemicals that would undergo testing.

The most significant barrier they had to overcome was also one of the project's strong points: the interdisciplinary nature of the panel. The BCCP project's subject matter required the input of people with divergent areas of expertise, including breast cancer biology, chemicals policy, toxicity testing, epidemiology, and breast cancer advocacy. They bridged the gaps by providing a primer of background reading materials, as well as introductory presentations at the meetings. The Co-investigators actively facilitated the meetings to continually articulate the project framework and focus the group's deliberations on the project goals. A Core Advisory Group met monthly to develop the ideas produced by the full panel and bring products back for discussion and refinement. The panelists expressed great satisfaction in having participated in this multidisciplinary project and in the accomplishments.

The primary outcome of the BCCP project was the Hazard Identification Approach (HIA), a recommended method for testing a chemical's effect on a variety of endpoints in biological processes that, if altered, could affect breast cancer risk. A final published report described the project rationale, process, and findings, including the biological pathways associated with breast cancer risk and the HIA. The Panel concluded that chemical toxicity testing—and the public policies that require it—can serve as a critical tool in breast cancer prevention, providing a practical basis for reducing potentially harmful exposures. The findings are summarized in four recommendations:

1. Chemicals must be tested for their possible impact on breast cancer risk and include the following endpoints: cell cycle changes; genotoxicity; endocrine disruption (e.g., estrogenicity); and altered mammary gland development.

2. To accurately evaluate the potential of a chemical to raise the risk of breast cancer, toxicity tests must be designed and conducted with the understanding that a chemical's effects vary depending on timing of exposure and underlying susceptibility factors.
3. Research needs to:
 - Further elucidate biological processes;
 - Adapt current toxicity testing methods to be more relevant to breast cancer; and
 - Develop and validate new toxicity testing methods, including high-throughput screening.
4. The process that this panel devised and carried out could be applied to other disease endpoints in order to develop a comprehensive approach to identifying chemicals that pose a risk to human health.

The final report "Pathways to Breast Cancer: A Case Study for Innovation in Chemical Safety Evaluation," an executive summary and other project information are available at: <http://coeh.berkeley.edu/greenchemistry/cbcpr.htm>.

**SUPPLEMENT:
2011**

Supplemental funding was awarded to the Co-investigators to advance the projects goals and disseminate the findings to targeted audiences. Three articles are being drafted by the leads and some Panel members for publication in peer reviewed journals to validate the scientific approach and provide a foundation for future efforts in breast cancer research and chemicals testing. The grantees will also translate the final report and the journal articles into lay document(s) and fact sheet(s) to inform policy and other efforts.

**PROGRESS:
2012**

As of May 2012, the topic areas of three articles were defined and outlined. Two of the three planned journal articles were in draft form, and the topic area of the third article was undergoing revision in light of other recent publications. Co-authors were identified from among the panel members, as were the journals to target for submission. As each article is revised it will be formatted for the target journal and submitted for publication.

Several potential science writers were identified to draft the lay materials, including a summary document and fact sheets. After the selection process, a writer will be contracted to produce the materials in preparation for additional dissemination of the project findings.

5. Making Chemicals Testing Relevant to Breast Cancer

RFP Goals

The original goals of this initiative were:

1. Identify and evaluate a comprehensive, cost-effective battery of assays for screening chemicals that incorporates the spectrum of mechanisms (tumor promotion, tumor initiation, tumor enabling and developmental disruption) by which chemicals are known or suspected to contribute to breast cancer.
2. Develop new testing methods and model systems for identifying and testing chemicals for their potential to contribute to breast cancer. An expert group was convened to review the RFP in light of the Breast Cancer and Chemicals Policy (BCCP) preliminary results. These reviewers included BCCP Panel and SRI Strategy Team members. They agreed to limit the scope of this RFP to the first initiative aim, developing tests

to screen chemicals for activity in biological mechanisms that play a role in breast cancer and to demonstrate the relevance of these tests for breast cancer using experimental cell based and animal models.

Application Process Results

In response to the Request for Proposals (RFP), CBCRP received eight applications and funded five. Interestingly, the review committee initially recommended funding four proposals and recommended not funding one, but was split about the merit of the remaining three. Those three were invited to revise their applications after receiving reviewer input; one was funded after review by the committee. One of the requirements of these awards is to collaborate with the other funded grantees. Details of their collaboration to date are in the last section of this report.

Funded Research

TITLE	A: Biologically Relevant Screening of Endocrine Disruptors
AWARD PERIOD	8/1/2011 – 7/31/2014
PRINCIPAL INVESTIGATOR	Shiuan Chen, PhD, Beckman Research Institute of the City of Hope
RESEARCH QUESTIONS	<p>The goal of this proposed research was to develop screening assays for identifying and testing chemicals with relevance to known and suspected causes of estrogen-dependent breast cancer.</p> <p>Findings from this and other laboratories were intended to allow the researchers to hypothesize that environmental chemicals play critical roles in modulating breast cancer through the estrogen receptor, aromatase and the ERR receptor. The researchers planned to develop functionally relevant assays that would allow the identification of environmental chemicals contributing to breast cancer.</p>

METHODS	<ol style="list-style-type: none"> 1. The researchers intended to refine a breast cancer-relevant high-throughput screening assay using a breast cancer cell line generated in their laboratory that was positive for all three important targets (ER, aromatase and ERR) of endocrine disruptors. 2. A set of breast cancer-relevant genes were to be tested for usage as markers to confirm the physiological importance of the chemicals identified from the screening assay. 3. Experiments were to be performed to identify additional novel markers for environmental chemical-mediated responses in breast cancer. 4. Animal experiments were to be performed to confirm the utility of the screening cell line and gene expression signature in the prediction of the effects of endocrine disruptors in the body.
PROGRESS: 2012	<p>During the first year, the team of investigators with research experience in breast cancer translational research, estrogen biology, bioinformatics analysis, and animal experiments has worked hard to develop a novel and breast cancer-relevant assay for the endocrine disruptor screen. They refined a breast cancer-relevant high-throughput screening assay using a breast cancer cell line generated in this laboratory that is positive for all three important biological targets (ER, aromatase and ERRα) of endocrine disruptors. The screening system has been adapted to a 1,536 well-format, thus they can screen 1,536 compounds each time. They tested the system with a collection of 466 compounds and have found some of them with the capacity to change the ability of breast cancer cells to produce estrogen and to affect estrogen function.</p> <p>Through collaboration with Dr. C. Teng and her colleagues at NIH, this laboratory's assay has been nominated and approved by the Tox21 project (a federal effort for environmental chemical screen.) Collaboration between scientists at City of Hope and those at the Tox21 community has been initiated to facilitate the development of innovative assays to identify chemicals that can contribute to breast cancer.</p>

TITLE	B: Xenoestrogen-Specific Perturbations in the Human Breast
AWARD PERIOD	9/1/2011 – 8/30/2014
PRINCIPAL INVESTIGATOR	Shanaz Dairkee, PhD, California Pacific Medical Center Research Institute

RESEARCH QUESTIONS

The collaborators on this project previously developed interactive processes to evaluate the effects of potentially carcinogenic chemicals on non-malignant human breast cells that could be studied experimentally. They had already demonstrated that environmental chemicals caused dramatic changes in cell programming, which are similar to the effects of estrogens. Since estrogens are involved in the origins of breast cancer, it is important to regulate the use of chemicals that mimic this hormone, also known as xenoestrogens (XEs). For example, the well-known carcinogen, diethylstilbestrol or DES, is an estrogen mimic and increases breast cancer risk.

The researchers hypothesized that continued exposure of non-malignant breast cells to XEs—at levels already reported in mother’s blood, cord blood, placenta, mother’s milk and human tissue—alters central functions of cell metabolism, and redirects exposed cells on the path to cancer.

METHODS

Using bisphenol A (BPA) as a test chemical, the researchers previously identified six sets of genes that allow damaged human breast cells to survive and acquire additional defects and predict functional deficiencies also found within aggressive breast tumors. They intended to build on these findings in 3 steps:

1. Define consistent changes caused by a wide panel of known XEs in non-malignant breast cells using established cell biology assays. This would establish a basic battery of tests to screen unknown chemicals, which might behave as XEs.
2. Apply novel technologies and computational approaches to enhance the understanding of XE-induced functional changes thereby facilitating the development of additional tests. This would allow an expanded choice of reliable screens from a comprehensive battery of assays for XE effects.
3. Apply the researchers’ ability to obtain significant data from small numbers of cells within clinical samples to develop assays utilizing readily renewable and repeatedly available sources of non-malignant breast cells such as human milk.

The researchers addressed scientific skepticism of why or how biological effects of XEs are relevant by identifying a series of simple metabolic functions that could define pertinent cancer related effects—or lack of effects—of a chemical on human cells. They showed that oxidative stress, metabolic pathway signaling, apoptosis, and proliferation consistently occurred after exposure of living cells to BPA and to methylparaben. Ascertaining these and other functional changes at the cellular level provides the needed mechanistic framework for whole animal studies and advances standardized XE screening. To extend the study of tiny samples from human breast tissue to the earliest steps of carcinogenesis, and to establish other sources of breast epithelium, they proposed to optimize techniques they had already used to grow stem cells present in human milk.

**PROGRESS:
2012**

During the initial funding period, a total of 6 non-malignant HRBEC lines, and breast cancer cell lines were exposed to test XEs at concentrations encompassing levels encountered in human body fluids. To date, a total of 270 exposure conditions including multiple non-XE controls were implemented. Fractions from each test condition were collected towards the analysis of rapid changes in candidate gene expression, and quantitative shifts in relevant gene products. Functional response measurements of cell death evasion and cell cycle distribution have also been completed for the entire sample set. Based on the most significant criteria identified, future goals involve validation studies with HRBEC samples from several individuals.

TITLE

C: Cell Bioassays for Detection of Aromatase Gene Activators

AWARD PERIOD

8/1/2011 – 7/31/2014

PRINCIPAL INVESTIGATOR

Michael Denison, PhD, University of California, Davis

RESEARCH QUESTIONS

Researchers for this study proposed that new methods are needed for testing chemicals for their potential to contribute to breast cancer, in this case examining aromatase promoters.

Are chemicals capable of activating the breast cancer-relevant aromatase promoters PII, I.3, I.4 and I.7, thus increasing the risk of developing hormone-dependent mammary tumors? How can this be detected?

METHODS

This project proposed to construct breast cancer cells that contain the 4 promoters of aromatase coupled to a luciferase gene. The researchers proposed that these cell constructs would be able to produce light upon exposure to chemicals that stimulate the activity of one or more of these promoters. Increased aromatase promoter activity results in increased expression of mammary aromatase, production of estrogens and ultimately stimulation of hormone-dependent mammary tumors.

Aromatase promoter gene sequences for PII, I.3, I.4 and I.7 were to be coupled to the gene for the enzyme luciferase which, upon stimulation, produces light. These constructs were to be incorporated into the DNA of commercially available breast cancer cell lines. These stably transfected cells would be characterized and validated by determining their response to compounds known to stimulate the activity of each of the inserted aromatase promoters. Cell constructs that respond to these compounds as would endogenous aromatase would be selected for the screening of various chemicals known or suspected to cause endocrine disruption, including pesticides, environmentally persistent chemicals (e.g. flame retardants), and chemicals used in large quantities in industrial processes or consumer products (e.g. phthalate plasticizers, bisphenol A, etc.)

**PROGRESS:
2012**

Aromatase-specific promoter-luciferase reporter gene DNA plasmids containing promoters p11, p1.3 and p1.4 were obtained and its DNA sequence confirmed. The p1.7 promoter and its regulatory sequences are currently being isolated by recombinant DNA techniques. Insertion (i.e. transfection) of these plasmids into human breast and liver cancer cell lines revealed that all but one of these aromatase plasmids were active, albeit to a relatively low level; however, the aromatase promoter 1.4-luciferase plasmid exhibited elevated activity.

These studies demonstrate the feasibility of the proposed approach to generate aromatase promoter-specific screening bioassays. The functional activity of these aromatase promoter-specific luciferase reporter plasmids transfected into a wide variety of other breast cancer cell lines is currently being examined to identify the optimal cell line for bioassay development. Validation of these recombinant cell bioassays will involve comparisons to promoter-specific expression of endogenous aromatase activity and effects on estrogen synthesis and proliferation of breast cancer cells in vivo using method that were established in the current grant period. Additionally, they optimized cell culture and dosing protocols necessary for high-throughput chemical screening applications using these cell lines when they are optimized and validated.

TITLE	D. Biomarkers for Environmental Exposures in Breast Cancer
AWARD PERIOD	8/1/2011 – 7/31/2014
PRINCIPAL INVESTIGATOR	Zena Werb, PhD, University of California, San Francisco
RESEARCH QUESTIONS	<p>By developing improved mouse mammary tissue models that respond to critical doses of environmental agents, molecules that change as a result of the exposure can be identified. The researchers proposed that one category of molecules that might change were the sugars that modify proteins made by the breast tissue. Such sugar modifications are seen in breast cancer, and therefore their appearance in response to these chemicals could be the first harbinger of changes leading to breast cancer.</p> <p>The researchers hypothesized that environmental agents that increase the risk of breast cancer risk would alter the sugar modifications of proteins made by mammary cells.</p>

METHODS

The researchers proposed to use mouse and human breast tissues in 3D culture systems that model the development of the normal mammary gland. To assess the risk from these environmental chemicals, they planned to treat these tissues and look for abnormal development, and then look for the production of proteins that have altered their sugar modification.

This project was to use mass spectrometry to measure these modified sugars. The researchers assembled a multidisciplinary team of mouse and human breast biology and cancer and systems biology and regulatory toxicologists at California EPA. This team intended to focus on the perturbation of breast development by environmental chemical stressors in both mouse and human tissues in culture and in vivo.

The team proposed to use the mouse mammary organoid assay, which undergoes branching like real breast in a tissue culture model, to analyze potential various environmental agents. These agents may affect whether breast cells divide, branch or make milk proteins, whether they differentiate and may start the breast cells on the way to cancer. Their approach looked at the exposure-related changes in sugars that modify breast proteins by a special separation procedure, mass spectrometry. In looking for biomarkers, they hope to develop an assay for assessing exposure in girls and women. Many biomarkers with clinical utility in cancer already rely on modified sugars, making the team confident that they would be able to find such new biomarkers that could lead to specific tests.

**PROGRESS:
2012**

In the first year of funding this team successfully developed models using mouse breast tissues in conventional cultures and in three-dimensional (3D) organ-like cell cultures and shown that several prototype environmental chemicals alter the development of these tissues. To begin to develop tools to look for biomarkers that indicate exposures, they examined the carbohydrates made by the breast cells exposed to these environmental agents using proteins called lectins that bind to specific types of sugars. As an additional and novel approach they also initiated use of a novel computational approach to examine potential proteins with which the environmental chemicals might interact.

This team is currently further investigating the effects of environmental chemicals on the different cell populations that are involved in forming branched structures in organotypic cultures of primary mouse mammary epithelial cells using immunohistochemical markers. To date, they have found that both MECs and stromal cells have glycoproteins that carry carbohydrate structures that can interact with leukocytes, interesting since breast tumors often have immune cell infiltrates.

Overall, this team reported meeting initial goals for the first year. These studies are relevant for determining how environmental agents alter breast development and for identifying markers that could be valuable in assessing levels of exposure that might affect risk for breast cancer.

This investigator reported publishing work from this award: Ewald, A. J., R. Huebner, H. Palsdottir, J. K. Lee, M. Perez, D. M. Jorgens, K. J. Cheung, A. Tauscher, Z. Werb & M. Auer (2012). Mammary collective cell migration involves transient loss of epithelial features and individual cell migration within the epithelium. J. Cell Sci. [Epub 17 Feb] doi:10.1242/jcs.096875. PMID: 22344263.

TITLE	E. Building on National Initiatives for New Chemicals Screening
AWARD PERIOD	8/1/2011 – 7/31/2014
PRINCIPAL INVESTIGATOR	Chris Vulpe, PHD, University of California, Berkeley

RESEARCH QUESTIONS

The project responded to the findings of the CBCRP-funded Breast Cancer and Chemicals Policy project, which recommended development of novel breast cancer-relevant cell-based chemical tests (assays) that could be incorporated into regulatory testing programs and initiatives to design safer chemicals (green chemistry). The goal of this project is to identify the assays that help predict whether a chemical will cause mammary gland tumors in animals, allowing researchers to screen many chemicals and flag the most hazardous ones or others that need further study.

The researchers anticipated that cell-based (in vitro) chemical tests could be adapted and used to quickly and cost-effectively identify chemicals that may play a role in breast cancer. The EPA ToxCast assays evaluate many different mechanisms of action. However, these tests were not specifically designed to detect mechanisms relevant to breast cancer. By identifying the cell changes that occur frequently with exposure to chemicals known to cause breast cancer in laboratory animals, the researchers expect to be able to create a profile of a possible breast carcinogen.

METHODS

This project proposed to build on programs at the US Environmental Protection Agency (EPA ToxCast program) and the National Toxicology Program (NTP Tox21 program) that are developing rapid chemical screening methods to fill current gaps in chemical safety evaluation. Data from the EPA ToxCast and NTP Tox21 screening programs are to be used to prioritize chemicals for further evaluation and regulation, so it was important that they use breast-cancer relevant tests.

First the researchers proposed to select from chemical tests already validated by ToxCast, choosing the assays that are most relevant to breast cancer. They planned to transfer these tests into a variety of breast cell models that range in their complexity. They also proposed to develop two new assays (e.g. to measure changes in mammary cell specific enzymes involved in estrogen production) that are not part of the ToxCast program but that represent mechanisms likely to be important in breast cancer.

Second, the researchers proposed to run these assays on approximately 60 chemicals and compare the results of assays performed on chemicals not associated with breast cancer to the results of assays performed on known carcinogens. Several of the chemicals they selected for testing are associated with breast cancer risk in humans, but because there is more data available from laboratory animal studies, their analysis proposed to focus on animal carcinogens.

PROGRESS:
2012

In the first year of the project, this team made substantial progress on testing mammary carcinogens and noncarcinogens in a variety of in vitro tests using two different mammary cell models (MCF-7 and MCF10A). They finalized a list of 143 chemicals that to be tested, categorizing them as mammary gland carcinogens, mammary gland development disruptors, and chemicals that were not carcinogenic in long term tests at the NTP. Mammary gland carcinogens were further divided into more and less genotoxic. They made arrangements to obtain many of these chemicals from federal agencies involved in the Tox21. They updated their list of over 100 assays to use to test the chemicals to reflect the rapid technological advances occurring in the field and to maximize comparability with Tox21 test programs. They finalized testing protocols and conducted initial experiments with 9 chemicals in 11 assays at 13 dose levels.

In parallel with these efforts, the Yaswen laboratory continued its work to develop human mammary tissue models that better reflect tissue complexity. For example, they began developing 3-dimensional tissue models that will include mammary epithelial and stromal cells. These more complex models may be used for assays in later stages of this project. The Leitman laboratory conducted initial work in a human BT474 breast cancer line that expresses both ER alpha and HER2 pathways and they are evaluating use of these models in order to identify chemicals activating these pathways.

A project community advisory committee including representatives from women's health and breast cancer organizations as well as state and federal regulatory agencies and NIH, was formed and met in September 2011. The project was presented to the US EPA National Center for Computational Toxicology as part of efforts to ensure comparability of methods between these projects. One of the partners in this grant is also maintaining a website on this project: www.silentspring.org/our-research/chemicals-and-breast-cancer/tools-green-chemistry-high-throughput-screening.

BOTH ENVIRONMENT & DISPARITIES

6. Statistical Methods to Study Interacting Factors that Impact Breast Cancer

RFP Goals

- A. What statistical methods can best take into account the complexity of breast-cancer risk, including the likelihood that the effects of risk factors vary in combination with each other and over the life course?
 - a. What methods are most appropriate when variables often treated as confounders may, in fact, be on the causal pathway?
 - b. What methods are most appropriate to elucidate effect measure modification (interactions) involving more than two variables? What are the best methods for identifying effects of risk factors co-occurring across multiple domains, for example, chemical exposures in the presence of psychosocial stressors and/or susceptibility factors from early life?
 - c. What are the best methods for analyzing effects and exposures that may vary by life stage?
- B. What are the best methods for identifying joint effects (additive, synergistic, or higher-order effects) of multiple chemical exposures operating via a shared biological pathway (for example, endogenous plus multiple environmental estrogens)?
- C. What are the best methods for incorporating area-level measures of environmental, psychosocial, and other exposures to account for spatial variation, spatial auto-correlation, and multi-level effects?
- D. What relationships are revealed by applying the new methods developed in response to one or more of the other specific aims in existing data sets?
- E. What are the implications of complex statistical methods for the design of future studies: What kinds of exposure data and study populations are needed?

Application Process Results

In response to the Request for Proposals CBCRP received eight applications and funded three awards. The scientific review committee was asked to make a recommendation of a package for funding; they unanimously agreed upon two proposals and included one other with a contingency. One of the requirements of these awards is to collaborate with the other funded grantees. Details of their collaboration to date are in the last section of this report.

Funded Research

TITLE	A. Model-building with Complex Environmental Exposures
AWARD PERIOD	9/1/2009 – 8/31/2012
PRINCIPAL INVESTIGATOR	David Nelson, PhD, Northern California Cancer Center

<p>RESEARCH QUESTION</p>	<p>The overall goal of this proposal was to extend computer-intensive methods to complex cancer and environmental data sets.</p> <p>Can statistical data mining methods being developed to explore and discover associations and relationships in large, complex data sets be profitably applied to determining which, if any, of the thousands of pesticide compounds being used in California agriculture pose a risk of breast cancer?</p>
<p>METHODS</p>	<p>The researchers proposed to use data from a large, ongoing study to address an important public health topic: understanding the relationship between agricultural pesticide use and the occurrence of breast cancer, using two unique California resources. The first, the California Teachers Study, is an ongoing research effort begun in 1995 and involving over 130,000 active and retired California teachers. The second is California’s Pesticide Use Reporting System. This system has tracked every commercial application of over 1000 different agricultural pesticides throughout the state of California since 1990. The database contains information about the what, when, where, who, how, and how much, of every agricultural pesticide application in California. Integrating these data sets would provide a unique opportunity to evaluate the relationship between pesticide exposures and breast cancer. The researchers proposed to then use expert knowledge of pesticides to apply statistical data mining methods, and to determine whether these methods could do better than simpler, more traditional methods.</p>
<p>PROGRESS: 2010</p>	<p>The first year of this project focused on Aims 1 and 4, which called for the acquiring hardware and developing the multi-site software foundation necessary (1) to perform thousands of complex, high-dimensional simulations, (2) to aggregate and interpret the results of these simulations, and (3) to create easy-to-create and easy-to-read web-based systems for storing, retrieving, and publishing the expected mass of simulation data and results. The project was successful in meeting these first year goals. Researchers were then well positioned to proceed to the second year, which intended to focus on Aims 2 and 3. At the start of the second year, they were beginning to design and execute the simulations necessary to evaluate the efficiency of data mining approaches as a way to obtain robust measures of exposure importance (Aim 2).</p>
<p>PROGRESS: 2011</p>	<p>At the start of the second year, the researchers decided, based on the advice of reviewers, to expand the scope of the project to include databases of hazardous air pollutants available from the U.S. EPA and the California EPA. However, at the same time, a major barrier arose with the project’s exposure expert leaving, stalling progress on a priori classification of pesticide exposures. While an excellent exposure assessment professional was being hired, the second year was focused mainly on Aims 2 and 3.</p> <p>As of writing of the progress report, the researchers were midway through performing the simulations necessary to evaluate the efficiency of data mining approaches as a way to obtain robust measures of exposure importance (Aim 2). They had also begun designing and debugging the necessary sensitivity analyses to evaluate how critical the results were to issues of GIS parameterization and exposure assessment (Aim 3).</p>

TITLE	B. New Methods for Genomic Studies in African-American Women
AWARD PERIOD	9/1/2009 – 8/31/2012
PRINCIPAL INVESTIGATOR	Daniel Stram, PhD, University of Southern California
RESEARCH QUESTIONS	This project proposed to use innovative statistical methods to investigate genetic differences in breast cancer among African American women. The team hypothesized that new statistical methods and techniques could be applied to the African American Breast Cancer (AABC) data to better understand the relationship between disease risk and over 1 million measurements of genetic variation for each study participant.
METHODS	<p>The researchers proposed to develop statistical methods, and apply them along with other new and established methods to analyze the AABC study data. They planned to conduct computer-based realistic simulation studies (based on evolutionary simulation techniques) to determine which of the statistical techniques could be expected to give the best results with real data.</p> <p>The project proposed to evaluate and compare these to other methods. The analysis of the AABC data would also attempt to find new disease associations that would help understand differences in individual, genetic susceptibility to breast cancer.</p>
PROGRESS: 2010	<p>The grantee took two different paths related to haplotype based association testing. The first examined known regions carrying risk genes for additional association signals related to haplotypes beyond the known individual single-nucleotide polymorphism (SNP) associations. The second approach involves a whole-genome scan for haplotype associations. They conducted fine mapping of shorter linkage disequilibrium patterns in people of African ancestry by using genome wide association study (GWAS) data to estimate all common haplotypes in these regions and compute haplotype specific risk estimates.</p> <p>They also began refining a 3-step haplotype block-based approach to scanning for haplotype associations throughout the genome, irrespective of the location of known GWAS hits. When the global test passes a certain level then haplotype-specific risk estimates for each of the haplotypes are performed. Because both the four gamete rule and the global association test does not require phased data, they can be computed very rapidly (in comparison to more elaborate methods needed to estimate single haplotype-specific risks.</p> <p>So far there is little evidence that known copy number variants (CNV) are associated with breast cancer risk, based upon the probes presented on the Illumina 1M chip used for genotyping in the AABC. Comparison to CNV detection using Framingham Heart Study data showed a very poor level of agreement between calls of CNV polymorphism across platforms.</p>

**PROGRESS:
2011**

This group continued to use linkage disequilibrium and haplotype-based methods to fine map the weak associations seen with GWAS hits found in other populations and improve assessment of breast cancer risk in African American (AA) women. The risk score composed of risk alleles found by fine mapping was much more strongly predictive of risk in AA women than the score consisting of previously discovered GWAS hits in non-African derived populations. For example, AA women in the upper quintile of revised score had a relative risk of 2.1 compared to AA women in the lowest quintile. This relative risk is considerably larger than the 1.44 observed using only the “index” GWAS SNPs found in other populations.

Efforts to relate known CNVs which can be predicted using probes present on the 1M chip for genotyping in this study population have found little evidence that these known CNVs have any association with breast cancer risk. Even this null finding is interesting and a manuscript is currently in development.

This group is also continuing work on admixture and reuse of GWAS data. Currently they are examining how to estimate the fraction of the heritability of breast cancer that is captured by common SNPs in GWAS, applying methods used by others to this study population.

TITLE

C. Cancer Mapping: Making Spatial Models Work for Communities

AWARD PERIOD

9/1/2009 – 8/31/2012

PRINCIPAL INVESTIGATOR

Eric Roberts, MD, PhD, Public Health Institute

RESEARCH QUESTIONS

Data is vital to ascertain breast cancer burden and also to explore possible patterns or causes. This project sought to create new approaches and tools to help communities understand and investigate breast cancer data.

The research questions for this project fall into three overlapping areas.

- The geography of invasive breast cancer in California: Can communities that face heightened vulnerability to invasive breast cancer be geographically defined? Is risk related to issues of social class or segregation?
- Implementation of statistical methods: How can the work of statistical researchers be adapted to the needs of diverse stakeholders in order to carry out mapping?
- Communication and utility for translation: How do stakeholders work through issues related to the uncertainty around detecting “clusters” of disease? How should results be communicated? How to use maps in communication, advocacy, and public health action?

METHODS

To create a protocol for mapping breast cancer in a large, diverse state such as California, this project proposed to convene an Advisory Group (AG) of collaborators with diverse backgrounds and a multi-disciplinary project team to develop and refine a broadly applicable mapping protocol to help locate vulnerable communities, understand demographic risk factors, target prevention/intervention efforts, and generate hypotheses about breast cancer.

The technical staff planned to begin by working with “simulated data” to determine what kinds of disease patterns (in terms of geographic size, shape, and degree of risk) the methods could locate. This information would be crucial for the AG to make decisions about how the methods should be used. During this time, the health educator would work with the AG to identify group learning objectives and capacity building necessary for decision-making. Key technical decisions regarding the mapping protocol were to be directly informed by AG values and preferences. The AG would also help staff to develop supporting material so that advocates, communities, government, and other stakeholders could interpret breast cancer maps. Finally, the researchers planned to produce statewide, annualized maps showing areas of California with elevated risk of breast cancer.

PROGRESS: 2010

This group convened an Advisory Group (AG) of collaborators with diverse backgrounds and a multi-disciplinary project team to inform and implement this award. The health educator worked with the AG to identify group learning objectives and capacity building necessary for decision-making about the mapping protocols, tools and training needs. AG members have been actively and enthusiastically engaged in this process.

The technical staff created a simulated data set, to allow for testing of a variety of methods for determining what kinds of disease patterns (in terms of geographic size, shape, and degree of risk) each could locate. Staff ran various scenarios at different levels of geographic and temporal detail and presented a range of census tract-level maps of breast cancer incidence to the AG, so that they could make informed decisions about the methods and how they methods should be used. The key technical decisions regarding the mapping protocol were directly informed by AG values and preferences through an input iterative process.

The contribution of these stakeholders has been essential to adapting statistical and geographic methods into a mapping protocol that is suitable for use by the affected communities. The AG has also begun help staff to develop supporting material so that advocates, communities, government, and other stakeholders can interpret breast cancer maps.

Public health department staff members and breast cancer advocates have successfully outlined a method for mapping statewide surveillance data for the incidence of invasive breast cancer that best meets their needs. These methods were applied to real data with project staff working closely with AG members to interpret and synthesize results generated and develop effective communication products to share project findings with diverse community stakeholders. To incorporate communication priorities from a diverse AG, project staff facilitated ongoing meetings and discussions to allow for critical dialogue necessary to address potential challenges and build consensus around an appropriate communication strategy. Through regular evaluation data collected from the AG on the stakeholder engagement process, members reported that AG input was effectively integrated into project goals and outcomes.

The 12 AG members consistently participated and (a) reviewed breast cancer mapping protocols with respect to their sensitivity, specificity, and communication potential; (b) reviewed results generated through the application of AG-selected methods to actual Cancer Registry data; and (c) outlined appropriate communication strategies to report project findings to diverse community and public health stakeholders.

Staff employed the AG's preferred mapping method to temporally and geographically analyze invasive breast cancer incidence statewide. This produced a series of 13 maps (one for each year of available data) depicting areas potentially having elevated disease risk color-coded to indicate degrees of consistency, reliability, and likelihood for representing spurious results related to denominator limitations. The team provided training and capacity building to facilitate the AG's identification of limitations of mapping methods, interpretation of results, and determination of effective communication strategies. They also facilitated conference calls with AG and Cancer Registry staff to clarify current procedures, protocols and challenges in accessing sub-county breast cancer data to allow the AG to refine their priorities and strategies and to develop products that would both meet communities' information needs and reflect public agency realities.

The AG reviewed draft communication materials and further refined the communication strategy expected to consist of three companion pieces:

1. A journal article submitted to peer-reviewed journals on the statewide Scan Statistic analysis and the Advisory Group process
2. A report of the findings generated by the statewide Scan Statistic analysis including data and information on the areas identified as having potentially elevated breast cancer risk
3. A community toolkit to assist advocates in accessing and responsibly utilizing breast cancer surveillance data and information.

The methods developed in this grant were presented to and well-received by CBCRP's community-based participatory research trainee teams. A methods paper was submitted and accepted for publication in the Journal of Public Health Practice and Management (in press as of August 2012) and the report of findings is being printed.

7. Toward An Ecological Model of Breast Cancer Causation and Prevention

RFQ Goals

The goal is to extend an emerging new paradigm of environmental health—the paradigm of complexity—into breast cancer research. Individual health must be understood as dependent on biological mechanisms that are nested within communities, societies, and physical environments and which are governed by interactions between and within these levels. Rather than focus on a limited number of pathogenic factors in isolation from each other, an ecological model of human health examines the web of relationships among many variables operating at different levels of organization.

Specifically, then, this project will examine the breast, within relevant context, as an ecosystem. It would explore the hypothesis that breast cancer is an ecological disorder that does not arise from a single causal pathway but emerges from a constellation of environmental stressors, from molecular to global, that interact with the ecosystem of the breast and all other stressors in ways that create disease. In the case of breast cancer, factors within the web of causation may include gene expression, tissue architecture, hormonal signaling pathways, chemical contaminants, fetal programming, nutritional

status, immigration history, barriers to physical activity created by the built environment, the timing and pace of sexual maturation, exposure to sunlight and light at night, neighborhood cohesion, economic status, radiation exposure, and cultural attitudes about breastfeeding. Characterizing how these factors assist, potentiate, reinforce, disrupt, diminish, restrain, or otherwise influence each other is at the heart of this investigation.

Application Process Results

In response to the Request for Qualifications, we received four strong applications and made one award. The review committee was intrigued by the prospect of funding all four of them and comparing the results, or having the four teams work together, either before or after working independently, as each application was found to have unique valuable aspects that would have added to an overall project. Unfortunately, funding for this Initiative did not allow such an approach.

Funded Research

TITLE	New Paradigm of Breast Cancer Causation and Prevention
AWARD PERIOD	1/2/2009 – 1/1/2014
PRINCIPAL INVESTIGATOR	Robert Hiatt, MD, PhD, MPH, University of California, San Francisco

<p>RESEARCH QUESTIONS</p>	<p>Specific questions to be answered included:</p> <ul style="list-style-type: none"> • What risk and protective factors should be included in a new, complex conceptual framework (e.g. gene expression, multiple contaminant exposures across the life course, fetal programming, the timing and pace of sexual maturation, personal experience of racism, neighborhood cohesion, etc.)? • How can dynamics of these factors be accounted for, including interactions, timing, dose, and other properties, in a visual manner?
<p>METHODS</p>	<p>This team proposed to conduct research and create a conceptual framework that would extend complexity theory to the study of breast cancer. They intended to include the perspectives of multiple disciplines to examine the web of relationships among the many variables operating on susceptibility, induction, and development of breast cancer.</p> <p>A multi-disciplinary expert panel was to assist the team in exploring alternative modeling approaches and generating a graphic display of the model that contains the necessary complexity and is transparent and understandable to the lay public. These were to be tested to ensure effectiveness and disseminated for further use and potential development and to inform research and prevention efforts.</p>
<p>PROGRESS: 2010</p>	<p>The project progressed smoothly and as planned. The researchers held two meetings of all experts on their multidisciplinary panel and plan a third and final one on April 13, 2010. Between meetings, core faculty collected myriad information on the nature and strength of relationship between factors leading up to breast cancer and developed a draft model that they planned to test and discuss in their third meeting. In all interactions there was open and thoughtful exchange of ideas about the causes of breast cancer even though there were honest differences of opinion about the relative importance of these factors. Simultaneously, they explored optimal ways to illustrate our new model, intending to use web-based technologies, and also ways to disseminate their work to a broad audience in ways that were transparent and understandable to the lay public. Products of this project were to include a web-based model (hopefully interactive), a final report and one or more publications in key scientific journals.</p>

PROGRESS:
2011

As of the end of April 2011 the project has completed a conceptual model in the form of an annotated illustration of selected causal factors and their interactions. These causal factors were divided into four domains: 1) biological, 2) physical and chemical environment, 3) lifestyle, and 4) sociocultural environment.

The researchers presented the model to multiple audiences from the lay public to scientists and had positive responses to the work. They were still working on the mathematical aspects of the model that relate a selected subset of the variables from the full conceptual model to each other in a dynamic, interactive way. The products of this project were to include one or more publications in key scientific journals and a web-based model that could be posted on the CBCRP website.

The model was featured in the recent IOM Report on Breast Cancer and the environment (pp. 179-180) http://books.nap.edu/openbook.php?record_id=13263&page=179; http://books.nap.edu/openbook.php?record_id=13263&page=180.

8. Environmental Causes of Breast Cancer Across Generations

Directed Research Goals

Many chemical compounds are known to affect fertility, birth outcomes and immune function and are thus suspected causes of or contributors to breast cancer. However, no human study has been able to measure exposure in the womb, a time of vulnerability for the developing fetus. This study proposed to investigate how exposure to environmental toxins *in utero* is related to breast cancer risk using the unique data available in the Child Health and Development Studies project.

Application Process Results

The CBCRP negotiated this project under the guidance of SRI Steering Committee members to make a Program Directed Award. One of the requirements of this award is to collaborate with the other funded grantees. Details of the collaboration to date are in the last section of this report.

Funded Research

TITLE	Environmental Causes of Breast Cancer Across Generations
AWARD PERIOD	5/1/2009 – 4/30/2012
PRINCIPAL INVESTIGATOR	Barbara Cohn, PhD, Public Health Institute
RESEARCH QUESTIONS	This study proposed to test the idea that prenatal exposure to environmental chemicals increases the risk of breast cancer. Specifically, does risk increase with higher levels of the insecticide DDT, or polychlorinated biphenyls (PCBs) and the chemical that it breaks down into in the body, which is known to increase estrogen action and to cross over to the fetus more readily than the original PCB compounds.
METHODS	<p>Researchers proposed to advantage of a critical resource, one of the rare research projects that collected blood samples years ago and then tracked women later in life, the Child Health and Development Studies (CHDS) cohort. These women gave birth in the Bay Area between 1959 and 1967. Daughters of these women were to be surveyed to identify their risk factors and environmental exposures. Blood samples from when their mothers were pregnant were to be tested for the suspect chemicals to look for differences between those women with a breast cancer diagnosis and those without in their 40s, and between women of different race/ethnicity, education and geographic areas.</p> <p>CHDS granddaughters, who are now in young childhood and adolescence, when contemporary exposures to environmental chemicals can be captured at a vulnerable period of breast development, were also to be invited to participate with their mothers. This project also proposed to establish procedures for ongoing participant involvement in this project as the daughters and the granddaughters moved through the ages of breast cancer risk. An Advisory Committee consisting of cohort members was to help design study procedures, materials, review research objectives and disseminate findings.</p>

**PROGRESS:
2009**

The primary barriers overcome in the first year of this study were identification of all sub-contractors and addressing a budget shortfall by proposing alternative scenarios to CBCRP.

In collaboration with CBCRP, a scenario was chosen that preserved all study aims, while scaling down the number of home visits to collect contemporary blood samples. In 2009, the researchers made significant progress in setting up and meeting with their External Advisory Committee, developing their questionnaire, finding sub-contractors to administer the survey, the home visit, and process and archive the blood samples collected, developing a protocol for archiving samples and developing estimates for all costs. In addition they constructed a data base to keep track of study subjects, updated their computer systems to ensure confidentiality of study subjects, began website development, developed consent instruments, began the process of designing a project message that would engage the subjects and designed a way to coordinate this data collection with other studies also in progress in the CHDS.

**PROGRESS:
2010**

In close collaboration with the External Advisory Committee, the researchers made major progress on their primary aim for the year, the development of the daughter's cohort. After the loss of the interview contractor, the researchers contracted with Survey Research Group, affiliated with the State of California and the Public Health Institute.

Major accomplishments included: designing recruitment materials; applying for and receiving Human Subjects Approval for the contact and interview procedures; completing the study website; identifying the interview contractor; beginning the interviews; deciding on the eligibility criteria for a subset of daughters who would receive a home visit; designing a protocol for collecting biological samples; redesigning the data base to accommodate eligibility criteria; beginning to consider the process for returning subject assay results and the design of the home visit consent procedures for daughters and granddaughters.

This team also successfully competed for a companion NIH grant that added researchers and aims related to this project, including mammogram collection for daughters of women with breast cancer and assistance in designing report-back procedures for individual results of environmental chemical assays, which was not part of the original protocol.

**PROGRESS:
2011**

In 2011, the researchers made major progress toward completing the goal of re-enrolling women into the cohort. In 2011, 1642 women were enrolled in the telephone interview, and all recruitment materials for the home visit portion of the study were finished. The team also contracted with the home visit company and the laboratory that will store the collected biological samples; redesigned the database to accommodate home visit activities; and, with the help of the External Advisory Committee, began exploring methods for returning individual assay results. They also held several meetings with both the External Advisory Committee and the Participant Advisory Council that was formed in 2011 from a supplemental NIH grant. The Participant Advisory Council included CHDS study participants who were assisting with efforts to maintain the cohort by improving recruitment and retention methods.

9. Environmental Exposures & Breast Cancer in a Large, Diverse Cohort

Directed Research Goals

This Initiative was created by combining two SRI Concept Proposals (“A Multi-Level and Transdisciplinary Approach to Understanding the Contribution of the Environment to the Etiology of Breast Cancer” and “Augment the California Teachers Study to Elucidate Environmental Risk Factors for Breast Cancer”) to take advantage of the two studies identified by the SRI Strategy Team and Steering Committee as having unique potential for advancing the field. This created a single competitive process for developing a scientifically sound research plan to leverage a large, on-going California cohort. The goal was to use data that already have been collected and gather additional data needed to (better) define the relationship between the chosen environmental contaminant(s) and breast cancer. The proposed research had to include well-defined social, cultural, geographic and/or demographic risk or protective factors that may influence breast cancer risk independently of, or

in some combination with, the environmental exposure(s).

Application Process Results

CBCRP offered the two candidate organizations pilot funding to develop a full proposal; one of the candidates submitted for and received a pilot award. A Scientific Advisory Committee (SAC) was convened by CBCRP to provide guidance and technical assistance to invited investigators. The SAC worked separately with each of the applicants, their staff and CBCRP staff to provide advice on prioritizing research goals, develop a study design and other aspects of the proposal development. Both candidates submitted applications. One proposal was found to lack scientific merit; the other was given a high scientific score and was funded. One of the requirements of this award is to collaborate with the other funded grantees. Details of the collaboration to date are in the last section of this report.

Funded Research

TITLE	Persistent Organic Pollutants (POPs) and Breast Cancer Risk
AWARD PERIOD	12/1/2010 – 11/30/2015
PRINCIPAL INVESTIGATOR	Peggy Reynolds, PhD, Cancer Prevention Institute of California
RESEARCH QUESTIONS	The primary objective of this study was to investigate the risk of breast cancer associated with both the older and newer POPs among participants in the California Teachers Study (CTS), a large on-going study of breast cancer among 133,479 female California professional school employees. The researchers also proposed to look for disparities in, and predictors of, body burden levels of these compounds and explore potentially important windows of susceptibility.

METHODS

Capitalizing on the unique resources collected over the 15 years since the CTS' inception, this study proposed to measure the levels of POPs in blood collected for two studies already underway. To identify disparities in, and predictors of, body burden levels of PBDEs/BFRs, the researchers proposed to utilize the approximately 360 blood specimens to be collected from CTS participants in 2010. A geographic information system (GIS) was to be used to link the residential location of CTS members' homes to the location of waste processing and manufacturing sites that may serve as sources of polybrominated diphenyl ethers/ brominated flame retardants (PBDE/BFR) exposures. Survey and census data was to be used to explore behavioral and sociodemographic predictors of body burden levels. Study participants are racially and ethnically diverse and from both rural and urban areas, so that analyses was intended to identify disparities in exposure to these compounds.

These preliminary analyses would help the researchers optimize selection of study subjects for the breast cancer risk analysis. This would be conducted among 2,000 CTS participants who have provided a blood specimen, 1,000 who will have been diagnosed with breast cancer and 1,000 women who remained breast cancer-free (controls) between 2007 and 2013. Concentrations of 15 PCBs, 4 organochlorine pesticides, 11 PBDEs, and 10 BFRs were to be measured in their blood. Statistical models were to be used to compare the levels of these POPs in women with breast cancer to the control women. Survey information was to be used to account for differences in other known risk factors. Additional analyses would evaluate whether certain women may be especially susceptible to risks associated with these exposures due to the type of tumor they have, or by virtue of selected behavioral or genetic characteristics. For a subset of the CTS cohort, the researchers proposed to use questionnaire and birth file data to enhance exposure estimates for earlier time periods that may represent windows of increased vulnerability to the effects of these compounds.

PROGRESS: 2011

Activities during the first year of this study primarily focused on the following start-up tasks: obtaining IRB approvals; coordinating with collaborating study sites to set up protocols for the selection and delivery of biospecimens from the CTS parent study to our laboratory; laboratory set-up and bioassay pre-processing of initial samples; acquisition of data files for record linkages; and the conduct of preliminary record linkages. Pilot record linkages were very successful and informative towards optimizing the researchers' final linkage strategies.

The primary obstacle encountered in the first year of the study was the delay in delivery of biospecimens to the researchers' lab from the CTS parent grant. Specimen collection began in May 2011 and, as of this progress report, they had received 90 blood samples designated for their first specific aim, and 487 samples (256 cases/231 controls) for their second specific aim. The first batch of these specimens underwent preprocessing and the bioassays were poised to begin in December 2011. Since completion of their specific aims is contingent upon the body burden measurements in the blood samples, the researchers had no experimental results to report at the time of this progress report. The researchers proposed that the next year of this study would be devoted to completing the record linkages, developing protocols for assigning indoor and outdoor measures of exposure, and conducting the laboratory bioassays on the blood samples as they become available.

REQUIRED INVESTIGATOR COLLABORATIONS

Epidemiologic Studies and Statistical Methods Meeting

The RFPs that the SRI program released routinely called for collaboration with other grantees, particularly in the case of initiatives with multiple awards. In order to facilitate the exchange of ideas, CBCRP staff arranged meetings of grantees and others. Following are descriptions of the exchanges to date. On February 7, 2011, CBCRP hosted a meeting of the funded large epidemiologic studies (California Breast Cancer Survival Consortium, Persistent Organic Pollutants and Breast Cancer Risk and Environmental Causes of Breast Cancer across Generations) and the statistical methods awards. The goals of this meeting were to 1) Cross-fertilize ideas between studies and grantees to inspire use of new or different methods and approaches in current studies; 2) Match statistics grantees' expertise and experience with cohort study grantees' research design and analytical approaches for possible consultation or collaboration; and 3) Inspire new SRI-related research topics and collaborations.

New tools and approaches were presented by other SRI grantees, explaining the Chemicals Policy approach and Demographics Questions tool, followed by summaries of the large epidemiologic studies and the Statistical Methods awards. Time was then allotted for each of the epidemiologic study teams to meet with each of the statistical grantees to discuss the analytical methods of the large study, future research directions for the study (or studies) and future SRI funding possibilities. All 18 of the participants submitted an evaluation; all found the meeting useful for their project and for networking and most had a clear sense of actions they could take from the meeting.

Chemicals Testing Grantees Meeting

The RFP stated "Applicants should be prepared to collaborate with the chemicals policy panel initiative members and other investigators funded under this initiative. At a minimum, this will include presenting ideas, approaches and findings at a semi-annual meeting, and offering feedback to other researchers on their work. Investigators from other CBCRP-funded projects and outside experts may also be invited to these meetings.

CBCRP staff organized the first meeting of the funded Chemicals Testing grantees on 6/6/12. The goals of the day-long meeting were to: 1) Cross-fertilize ideas between studies and grantees to inspire new or different methods and approaches in current studies and ideas for future research; 2) Review Chemicals Policy award findings, explore implications of currently funded research for policy, explore additional data needs for California and federal policy-making; and 3) Inspire new SRI-related research topics and collaborations.

The five funded Chemicals Testing awards were represented by eleven grantee team members. Three advocate members of one grantee's advisory committee also attended. The co-investigators of the Chemicals Policy award also presented and participated. The meeting kicked off with a presentation by Lauren Zeise of the California EPA, to frame the policy needs. Each of the awards was introduced, with a summary of the project and work to date, followed by lively discussion. The meeting ended with brainstorming future research needs and funding directions. Of the 13 evaluation submitted, all felt that hearing about other projects was interesting and useful and that the meeting was helpful for networking or developing possible collaborations. Participants offered many ideas for the December 2012 and May 2013 meetings.



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