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Authors

Sutton, P
Kavanaugh-Lynch, MHE
Plumb, M
[et al.](#)

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California Breast Cancer Prevention Initiatives: Setting a research agenda for prevention

P. Sutton^{a,*}, M.H.E. Kavanaugh-Lynch^b, M. Plumb^c, I.H. Yen^d, H. Sarantis^e, C.L. Thomsen^b, S. Campleman^b, E. Galpern^c, C. Dickenson^a, T.J. Woodruff^a

^a University of California, San Francisco, Program on Reproductive Health and the Environment, 1330 Broadway, Suite 1135, Oakland, CA 94612, USA

^b California Breast Cancer Research Program, University of California, Office of the President, 300 Lakeside Drive, 6th Floor, Oakland, CA 94612-3550, USA

^c Plumblin Consulting and Coaching, 541 South 52nd Street, Omaha, NE 68106, USA

^d University of California, San Francisco, 3333 California Street, San Francisco, CA 94143, USA

^e Commonweal, P.O. Box 316, Bolinas, CA 94924, USA

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ABSTRACT

The environment is an underutilized pathway to breast cancer prevention. Current research approaches and funding streams related to breast cancer and the environment are unequal to the task at hand. We undertook the California Breast Cancer Prevention Initiatives, a four-year comprehensive effort to set a research agenda related to breast cancer, the environment, disparities and prevention. We identified 20 topics for Concept Proposals reflecting a life-course approach and the complex etiology of breast cancer; considering the environment as chemical, physical and socially constructed exposures that are experienced concurrently: at home, in the community and at work; and addressing how we should be modifying the world around us to promote a less carcinogenic environment. Redirecting breast cancer research toward prevention-oriented discovery could significantly reduce the incidence and associated disparities of the disease among future generations.

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1. Introduction

As Alice Stewart, epidemiologist and discoverer of the link between *in utero* exposure to ionizing radiation and childhood cancer observed, “the best way not to see something is not to look for it” [1]. We know too little about breast cancer and the environment because historically scientific challenges and non-scientific economic, social and political forces have put the environment out of sight and out of mind [2].

Prevailing models of scientific inquiry are ill-suited to uncovering the complex web of circumstances leading to clinically apparent breast cancer [3–5]. While breast cancer arises from a convergence of the environment and genes, [6] most research has explored one or the other factor. Environmental influences on health encompass neighborhood and social factors such as racism and the physical and chemical exposures where people live, work, and play [5]. Yet most epidemiologic studies of breast cancer have focused on a narrow range of discrete behaviors or exposures, rather than the

confluence of these interconnected factors [4,7–9]. Such a convergence may in part explain the fact that African American women are three times more likely to be diagnosed with triple negative cancer than White or Latina women [10] and at younger ages [11]; that African American women diagnosed at the same stage as Non-Latina White women have poorer survival outcomes [12]; and that in general, breast cancer in racial/ethnic minority populations appears to have a poorer prognosis [13].

Moreover, despite increasing human exposure, the role of toxic chemicals, pollutants and other similar agents has been only marginally explored. Since 1945, chemical production has increased more than 15-fold [14]. In the United States, approximately 700 new chemicals are introduced into commerce each year and more than 84,000 chemical substances are listed by the US Environmental Protection Agency for manufacturing, processing or importation [15,16]; 3000 of these chemicals are used or imported in high volumes (greater than 1 million pounds) [15]. Every day everyone is exposed to environmental chemicals in air, water, food and consumer products. Yet the overwhelming majority of chemicals, including those identified as animal mammary carcinogens or endocrine disrupting compounds, have never been examined in an epidemiologic study of breast cancer, nor been included in an animal cancer bioassay [17,18].

* Corresponding author. Tel.: +1 510 350 1244.

E-mail address: suttonp@obgyn.ucsf.edu (P. Sutton).

Breast cancer research exploring exposure to chemical mixtures, critical windows of susceptibility, and environmental agents with the capacity to modify known risk factors are largely lacking [19]. And yet, history has provided us with experiments that document that early life exposure to environmental agents can have a profound impact on breast cancer, i.e., diethylstilbestrol (DES), ionizing radiation from the atomic bomb, and DDT [20–22].

Globally, funding to investigate prevention in general and avoidable environmental exposures specifically represents a small fraction of the resources directed to cancer research [23] (Fig. 1). This trend is mirrored in the United States, where only 6.5% of the National Cancer Institute's (NCI's) \$5.1 billion 2011 budget request was allocated to "cancer prevention and control" [24]. A federal interagency review of breast cancer and the environment found that at most, 10–11% of breast cancer research projects funded by the National Institutes of Health (NIH) and the US Department of Defense focus on environmental health and that no other federal agency supports substantial research on the environmental causes of breast cancer [6].

Thus, we have looked neither well nor hard for the role of the environment in breast cancer etiology. The gap produced by these limitations in the research has led many to believe that the environment plays little to no part in disease etiology. For example, the NCI's breast cancer prevention advice to patients downplays environmental etiology, stating "studies have not proven that being exposed to certain environmental exposures (such as chemicals, metals, dust, and pollution) increase the risk of breast cancer" [25].

Times are changing. Over the past few years, calls for shedding light on cancer and the environment have come from influential entities, including the Institute of Medicine, [3] the President's Cancer Panel [8], the federal Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC), [6] and the Agency for Toxic Substances Disease Registry with the US Centers for Disease Control and Prevention's National Center for Environmental Health [26]. A critical observation common to these diverse reports is that the environment represents a vastly underutilized pathway to prevention. As the IBCERCC stated, "By urgently pursuing research, research translation, and communication on the role of the environment in breast cancer, we have the potential to prevent a substantial number of new cases of this disease in the 21st century" [6]. The California Breast Cancer Research Program (CBCRP) is doing just that. Below we describe a four-year initiative to set a research agenda that will illuminate the links between the environment and breast cancer and uncover opportunities to prevent disease.

2. The California Breast Cancer Research Program

The CBCRP is the nation's largest state-funded breast cancer research effort and among the largest breast cancer research funders in the world. The CBCRP was founded in 1993 by the California legislature and through the efforts of breast cancer activists, scientists, clinicians, state legislators, and University of California officials [27]. The CBCRP is funded by a state tax on tobacco products, voluntary state personal income tax form contributions and individual contributions.

The CBCRP's program funding recommendations and strategic planning are the responsibility of the Breast Cancer Research Council (Council), a group of 15 people chosen to represent those affected by breast cancer and the institutions that can help find a solution. CBCRP supports new approaches that other agencies may be reluctant to fund. Since 1994, the CBCRP has awarded more than \$235 million in 966 grants to 107 institutions across the state.

Subsequent to a comprehensive review of CBCRP's research portfolio, in March 2004, the Council dedicated 30% of funds

between 2004 and 2009 to the coordinated, directive, collaborative Special Research Initiatives (SRI) to support research that addressed:

1. The identification and elimination of environmental causes of breast cancer; and
2. The identification and elimination of disparities/inequities in the burden of breast cancer in California.

The goal of the SRI was to fund research that not only increased knowledge about these questions, but also pointed to solutions that would reduce the suffering from breast cancer and move science closer to eliminating the disease. In total, 21 grants totaling \$23 million were awarded to address the environmental causes of breast cancer and the unequal burden of the disease [28].

In March 2010, after another thorough programmatic review, the Council built on the existing SRI by expanding the scope and devoting 50% of its research funds during 2011–2015. This new effort was titled the *California Breast Cancer Prevention Initiatives* (CBCPI). They committed an anticipated \$24 million to directed, coordinated, and collaborative research to pursue the most compelling and promising approaches to:

1. Identify and eliminate environmental causes of breast cancer.
2. Identify and eliminate disparities/inequities in the burden of breast cancer in California.
3. Population-level interventions (including policy research) on known or suspected breast cancer risk factors and protective measures.
4. Targeted interventions for high-risk individuals, including new methods for identifying or assessing risk.

Implementation of the CBCPI research agenda-setting began in 2010 and will be completed in 2015. This paper presents the CBCPI's methods and results of efforts to date to identify key research questions addressing the four topic areas, and proposes future directions in research to lead to the prevention of breast cancer.

3. Materials and methods

An overview of the process of developing the research agenda for the CBCPI is presented in Fig. 2. The full details of the dynamic process for determining specific research questions to fund within the four areas were articulated in a Strategy Development Plan [29].

3.1. Public and scientific engagement

We convened three expert groups to provide leadership and scientific expertise for the CBCPI, a Steering Committee and two sets of Strategy Advisors, one focused on Environment and Disparities and the other focused on Population-Level Interventions and Targeted Interventions for High-Risk Individuals. To recruit these individuals, we identified areas of expertise needed and generated a list of scientists with relevant expertise. Public engagement in the process included advocate participants in the CBCRP Research Council, community participants in the three expert groups, and community participation in Stakeholder events.

3.2. Identifying pivotal research questions

We used the following qualitative and quantitative methodologies to review, analyze and compile the relevant scientific findings and research recommendations to inform the development of pivotal questions for the CBCPI.

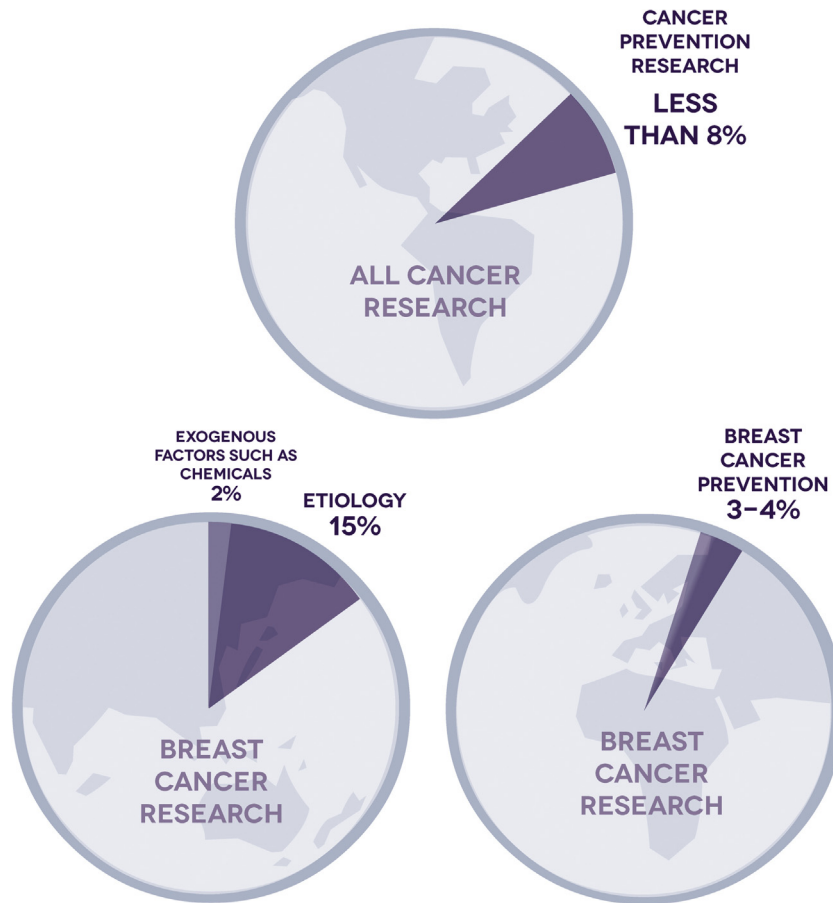


Fig. 1. Global research spending on breast cancer prevention and the environment (2008–2013). Data were compiled from the International Cancer Research Partnership, Cancer Research Funding from an International Perspective: Report from the International Cancer Research Partnership, 2012.

GOAL				
\$24 million dedicated to directed, coordinated, and collaborative research to pursue the most compelling and promising approaches to the environmental causes of breast cancer, disparities in breast cancer, population-level interventions, and targeted interventions.				
PUBLIC AND SCIENTIFIC ENGAGEMENT	IDENTIFIED PIVOTAL RESEARCH QUESTIONS	DEVELOPED CONCEPT PROPOSALS	CREATED FUNDING MECHANISMS	APPROACHES TO FUNDING
<ol style="list-style-type: none"> 1 Principal Investigator and Team^a 2 Twelve Steering Committee Members^a 3 Sixteen Strategy Advisors^b 4 Fifteen CBCRP Research Council Members 	<ol style="list-style-type: none"> 1 Targeted review of literature—23 targeted scans of topics 2 Review of 2004–2009 SRI Funded Projects 3 Interviews with SRI Principal Investigators and Strategy Team 4 Interviews with External Experts in Cancer Prevention 5 Stakeholder meetings, workshops, webinars 6 Science Assessments: Expert Assessments and Systematic Reviews 	<ol style="list-style-type: none"> 1 Identify and eliminate environmental causes of breast cancer 2 Identify and eliminate disparities/inequities in the burden of breast cancer in California 3 Population-level interventions (including policy research) on known or suspected breast cancer risk factors and protective measures 4 Targeted interventions for high-risk individuals, including new methods for identifying or assessing risk 	<ol style="list-style-type: none"> 1 Request for Qualifications 2 Request for Proposals 3 Program Directed Awards 	<ol style="list-style-type: none"> 1 Grants 2 Cooperative Agreements
DECISION-MAKING CRITERIA				
<ol style="list-style-type: none"> 1 Increase knowledge and solutions; 2 Truly transforming; 3 Community participation; 4 Coordinated approach; 5 Synergy; 6 Compelling to stakeholders; 7 Unique; 8 Feasible 				

Fig. 2. Overview of California Breast Cancer Prevention Initiatives 2011–2015. All four public and scientific groups engaged include a mix of scientists, advocates, clinicians and public health expertise. (a) Non-eligible for funding through initiative and (b) mixed eligible and non-eligible for funding through initiative.

3.2.1. Review of the literature

An initial step in the CBCPI process was to update the 2007 Gaps report “Identifying Gaps in Breast Cancer Research: Addressing disparities and the roles of the physical and social environment” [2]. This narrative review of the literature in 23 targeted environment and disparities areas was conducted by multiple experts, using a framework developed by Bigby and Holmes for studying how breast cancer differently impacts various groups of women [30]. For the update, we conducted “targeted scans” of the literature by searching PubMed for each of the 23 topics in the 2007 Gaps document to identify any substantive changes in the chapter’s findings and research recommendations. Details of the methodology can be found at http://cbrp.org/files/other-publications/2013_SupplGaps_Final.pdf.

We generally did not critique the included papers, but rather summarized the conclusions of the study authors. We then compiled the PubMed search findings in a list next to the “Summary and Future Directions for Research” sections at the end of each 2007 Gaps chapter to directly determine whether there was a “significant change” in the state of the science. A significant change was defined as one that could fundamentally shift the questions originally posed in the Gaps document and assist in focusing the CBCPI research agenda.

3.2.2. Review of 2004–2009 SRI funded projects

We compiled a summary of the results of SRI efforts in order to identify additional potential follow-on research questions and/or questions identified in the SRI but not funded [28]. This summary included: the RFP or RFQ goal, the application process results, and a description of the funded research and progress to date.

3.2.3. Interviews with SRI Principal Investigators and Strategy Team

We interviewed the Principal Investigators funded through the SRI and SRI advisors (advocates, clinicians, policy makers, and scientists from within and outside California) using a semi-structured interview. We solicited their suggestions for additional research topics in light of the progress or outcome of SRI efforts and/or other advances in the field that had occurred since the SRI was undertaken. We conducted data analyses using two methods: hand sorting and classification in MS Word, and auto coding according to interview question using NVivo 9 qualitative software. In order to determine the major themes from each interview question, we uploaded each unique response from NVivo into a spreadsheet and analyzed across interview questions.

3.2.4. Interviews with cancer prevention experts

We conducted individual semi-structured interviews and held small-group meetings at the American Association for Cancer Research’s (AACR’s) 2012 conference *Frontiers in Cancer Prevention Research* to solicit input from cancer prevention experts. We invited AACR conference speakers and co-authors to participate based on the intersection of their expertise with the CBCPI. In addition, we distributed a flyer inviting conference attendees to participate. The interviews and small group meetings began with a summary of the CBCPI, followed by an open-ended discussion of thoughts and ideas for the CBCPI research agenda. We recorded and transcribed the interviews. We used two methods for data analysis: hand sorting and classification in MS Word, and auto coding using NVivo 9 qualitative software. To identify major themes from each interview question, we uploaded each unique response from NVivo into a spreadsheet and analyzed across interview questions.

3.2.5. Stakeholder input

Stakeholders were engaged through representation by advocates on the CBCPI Steering Committee and both Strategy Advisor

groups. We also engaged a broad range of stakeholders through webinars, web-based surveys, CBCRP newsletters and website, and in-person meetings across the state as follows: (1) in 2011, CBCRP conducted workshops in eight different areas of the state, gathering research recommendations and priorities; (2) in 2012, 2013 and 2014, we solicited input during 1-h stakeholder webinars; and (3) in 2013, we presented CBCPI ideas to participants attending the CBCRP Symposium. During the in-person Symposium and webinars we compiled input through online ballots. We synthesized stakeholder input from all of the workshops, webinars and Symposium into research questions and major themes.

3.2.6. Science assessments

We commissioned science assessments on topics that the Steering Committee deemed to be of high interest but for which they needed additional information to make a decision about whether and/or how to move forward on the topic.

3.2.7. Concept proposals

The Steering Committee vetted the research questions identified through all of the above methodologies based on *a priori* decision-making criteria (Fig. 2). The Steering Committee prioritized specific research questions that were then developed into “Concept Proposals.” Concept Proposals outlined the rationale, objectives, methods, and estimated cost of pursuing each topic. Finally, we presented the Concept Proposals to the CBCRP Council for approval.

4. Results

4.1. Public and scientific engagement

A total of 26 individuals from across the US led or served as an official advisor to the CBCPI. The names and affiliations of these 26 individuals are provided in the Supplement in Appendices A and B. The Steering Committee members oversaw the CBCPI through video conference calls, in-person meetings and written communications with each other and with the Strategy Advisors. Approximately 300 stakeholders participated in the various stakeholder opportunities for input. All Concept Proposals were approved by the Steering Committee prior to submission to the Council.

4.2. Identifying pivotal research questions

4.2.1. Review of the literature

The results of the targeted scans of the literature were presented in 2013 as an online document, Gaps Supplement: Targeted Scans of the 2007 “Gaps” Document “Identifying Gaps in Breast Cancer Research: Addressing disparities and the roles of the physical and social environment” [31]. Overall, the results of the Gaps update found that the amount and relevance of research on the environment and disparities identified in 2007 varied a great deal in the subsequent five years.

Published research around the relationship between breast cancer and persistent organic pollutants (POPs) and bisphenol A (BPA) had increased. For other topics, such as pharmaceuticals, very little of the substantial research published since 2007 was related to breast cancer. A limited number of studies were found relevant to previously identified gaps in some topic areas, such as the need for specificity in definitions of neighborhood and community level variables (e.g., neighborhood socioeconomic status (SES), built environment and racial segregation). While a number of studies addressed the intersection of neighborhood racial composition and

neighborhood SES, they mainly examined how these factors affect breast cancer screening and treatment.

4.2.2. Review of 2004–2009 SRI funded projects

We compiled a detailed description of the 9 topics and 18 SRI funded projects [28]. The review of this document led to the identification of several “follow-on” opportunities, specifically on the topics of immigration, an ecological model of breast cancer and chemicals testing.

4.2.3. Interviews with SRI Principal Investigators and Strategy Team members

We interviewed 15 of the 20 Principal Investigators that received funding from the SRI; 1 individual declined to be interviewed; and 4 were unresponsive to 5 or more written requests. The following three research questions were found to have high (67%) agreement among Principal Investigators as topics to pursue:

1. Is there proof of concept that environmental chemical exposure during critical periods of development can induce or promote breast cancer in humans?
2. Does early life or founding generation exposures make you more susceptible to subsequent environmental exposures?
3. What are the key modifiable risk factors and conditions suggested by complex modeling systems?

Forty percent of the Principal Investigators stated that they believed that either investing in an existing cohort or supporting cross-disciplinary research teams were the best scientific approaches to addressing the research questions.

We interviewed 14 of 24 SRI Strategy Team members. The 10 individuals not interviewed included 4 who declined, 3 who were unavailable due to illness/sabbatical, and three already interviewed as SRI-funded Principal Investigators. The Strategy Team members' top priorities were:

1. Invest in an intergenerational cohort study, i.e., analyze how mother, daughter, and granddaughter respond to chemical exposures; and
2. Examine the relationship between environmental exposures and disparities across social class and race/ethnicity and incorporate a life course perspective or other time dimension into such analyses.

A cluster of responses targeted the need to improve and better utilize animal studies for indications of which environmental agents may be relevant to human health and to develop exposure assessment methods for chemicals and their metabolites suspected of adverse health impacts.

4.2.4. Interviews with cancer prevention experts

We hosted six discussions at the AACR including 2 focus groups; 3 one-on-one meetings; and 1 phone interview subsequent to the AACR conference. In total, 15 scientists participated in 1 of the 6 discussions. All discussions lasted between 60 and 90 min.

The theme that recurred in most of the discussions (four of six) was the need for trans-disciplinary research teams, or “team science”, to address CBCPI research questions. Ideas for immediate funding mentioned in one or more discussions were:

1. Improve knowledge of the windows of susceptibility relative to breast cancer risk;
2. Identify pathways controlling breast density;
3. Multiple questions about breast cancer and obesity;

4. Integration of animal and human models for understanding mammary development;
5. Breast cancer risk and biological effects on the breast from a variety of environmental exposures including stress, endocrine disrupting chemicals, and ionizing radiation from medical imaging;
6. *In utero* environmental exposures with the potential to influence hormones during pregnancy; and
7. Disparities in breast cancer incidence related to race, ethnicity, ancestry, and/or immigration status.

4.2.5. Stakeholder input

The statewide workshops resulted in a list of 144 research questions of interest to stakeholders. Of the 144 questions, 63 were rated “important” by two or more attendees. These questions are presented in the Supplement in Appendix C. There was statewide interest in research related to the geographic and temporal disparities in exposure to environmental chemical and social stressors, and to the range of cultural influences on breast cancer.

Of the 46 participants in our 3 webinars, 23 self-identified as staff/volunteers with breast cancer non-profit or other community-based organization; 15 as breast cancer or other researchers/scientists; 4 as interested members of the public; 3 as clinicians; and 1 as a non-breast cancer research scientist. The 25 stakeholders in the 2012 webinar provided 46 suggestions for CBCPI research directions. Major themes for research to fund that emerged included to:

1. Advance chemicals testing policy;
2. Understand the relationship between disparities in breast cancer relative to: environmental exposure to chemicals, the social determinants of health, geography, and workplace exposures; and
3. Disparities related to underserved and vulnerable populations.

The 2013 webinar involved 11 stakeholders who identified the “most compelling” topics to be: chemical exposures and prevention; hormones in the food supply; leveraging existing cohorts for opportunities to explore concurrent exposure to environmental and psychosocial risk factors for breast cancer; the impact of policy on breast cancer risk factors and incidence; and economic, housing, and education interventions. The 10 participants in the 2014 webinar reviewed themes under consideration in the population-level intervention topic area; no clear pattern of preference emerged among the participating stakeholders.

4.3. Science assessments

We engaged experts to conduct assessments of three issues in order to identify the most promising research questions on these topics:

1. Early Life Adversity and Breast Cancer (Disparities)

The review found preliminary evidence for an association between childhood adversity and risk for post-menopausal breast cancer, especially more severe forms of adversity, such as physical and sexual abuse. The most promising hypothesis identified was that the effects of childhood adversity are mediated by obesity, with proximal mediation by increased circulating insulin and enhanced local estrogen biosynthesis.

2. Experimental Studies of Breast Cancer and Stress (Disparities)

The review confirmed that very few studies have investigated environmental stressors and toxics exposure concurrently. Research is needed that tests different windows of susceptibility, applies stressors in a manner that can translate to human scale

ENVIRONMENT¹

- Explore windows of susceptibility to breast cancer from chemical exposures
- Quantify concentrations of hormones in beef in California
- Test (non-targeted) commercial chemicals in California's drinking water
- Assess occupational exposure to chemicals and breast cancer risk in California
- Reduce breast cancer risk through chemical safety testing*
- Develop a new paradigm of breast cancer causation and prevention
- Assess chemical exposures of women firefighters

DISPARITIES¹

- Explore racial/ethnic disparities in consumer product availability and use
- Assess the role of stress in race and ethnic disparities in breast cancer incidence and survival across California
- Understand the role of changes in biological, behavioral, social, psychological, and environmental factors that occur with immigration
- Conduct animal models to explore environmental and psychosocial exposures during windows of susceptibility and breast cancer
- Leverage existing cohorts for opportunities to explore concurrent exposure to environmental and psychosocial risk factors for breast cancer
- Explore psychosocial interventions on stress, depression and coping in relation to addressing breast cancer
- Identify connections between early life adversity and the risk of breast cancer (Pending)

POPULATION-LEVEL INTERVENTIONS²

- Develop policy interventions that can reduce or eliminate exposures to chemicals linked to breast cancer
- Identify effective population-level interventions to increase physical activity (Pending)
- Build a public health case for primary prevention of breast cancer
- Prevent exposure to ionizing radiation from medical imaging

TARGETED INTERVENTIONS FOR HIGH-RISK INDIVIDUALS²

- Improve risk assessment research to identify high-risk individuals
- Explore markers of individual breast cancer risk

Fig. 3. California Breast Cancer Prevention Initiatives topic areas for funding. (1) Except as noted, these topics have been approved by the California Breast Cancer Research Program's (CBCRP) Research Council. (2) These topics have been approved by the California Breast Cancer Prevention Initiatives Steering Committee for consideration by the CBCRP Research Council. (*) This project would build on: Schwarzmann M. and Janssen S. 2010. Pathways to Breast Cancer: A Case Study for Innovation in Chemical Safety Evaluation. University of California, Berkeley. <http://coeh.berkeley.edu/greenchemistry/cbcrcpdocs/pathways.report.pdf>.

or is clinically relevant and investigates the effects of chronic stress exposure.

3. Hormones in Food (Environment)

The review summarized the current use of veterinary drugs in food animal production and the concern that this practice may expose consumers to hormonally active substances. The reviewers found that whether the use of one or more of these drugs poses a human health risk remains subject to debate, fueled in part by formidable data gaps in understanding toxicity, exposure and ultimately the potential health risk of hormones in food. The expert assessment concluded that the available data do not permit an evidence-based, quantitative characterization of breast cancer or other health risks resulting from the use of hormonal drugs in food animal production.

We also solicited systematic reviews on: environmental chemical exposure and policy interventions; and interventions to reduce exposure to ionizing radiation from medical imaging. We anticipate these results will be submitted for publication by the end of 2014 and will be used to guide the development of Concept Proposals on these two topics.

4.3.1. Concept proposals

The CBCPI research agenda established to date encompasses 20 topic areas: 14 related to environment and disparities and 6 addressing population-level interventions and targeted interventions for high-risk individuals (Fig. 3). For these 20 topics, 14 Concept Proposals have been approved by the CBCRP Council.

5. Discussion

We undertook a four-year comprehensive effort to set a research agenda related to breast cancer, the environment, disparities and prevention. Stakeholder involvement was a key component of the

SRI and continued to be in the CBCPI, as is the case in all CBCRP projects. There was a consistent call for involving communities in CBCPI-funded research.

We identified common major themes raised by stakeholders and scientists from a variety of fields, including that the research agenda should: (1) advance complexity, i.e., “ecological” approaches that reflect the interconnectedness of peoples’ lives in contrast to a reductionist “risk factor” model; and (2) pursue “team science” in order to link the necessary systems of knowledge creation required to successfully conceive, design, and implement an ecologically based research agenda. To this end, we identified many administrative and cultural barriers among scientific disciplines and institutions that must be overcome if team science in breast cancer research is to become the norm. These include time and funding levels that do not support collaboration; administrative barriers to shared funding; competitive nature of scientific discovery; lack of common language; etc.

Our findings were also consistent with recommendations for improved research on cancer, the environment and/or prevention advanced in reports released by the Institute of Medicine, [3] the President's Cancer Panel, [8] the federal Interagency Breast Cancer and Environmental Research Coordinating Committee [6] and the Agency for Toxic Substances Disease Registry with the U.S. Centers for Disease Control and Prevention's National Center for Environmental Health [26]. Together, our findings and the call to action represented in these reports document an increasing groundswell for redirecting breast cancer research toward prevention that could significantly reduce the incidence and associated disparities of the disease among future generations.

Our findings are distinct from the agendas recommended in these other reports in our emphasis on the public health approach to disease prevention. Rather than asking what individuals can do to modify risk the CBCRP agenda asks how we should be modifying the world around us to promote a less carcinogenic environment.

Notably, CBCRP defines environment as “all of the non-genetic factors that might lead to breast cancer that are also largely outside an individual’s control.” Such a definition creates a huge shift in perspective, making it transparent how societal decisions shape individual behavior and circumstances.

The CBCRP’s nascent efforts represent a concerted attempt to spark a transformation of the environment and breast cancer research agenda overall (Fig. 3). Specifically, the CBCPI research agenda reflects that breast cancer arises from a complex system and that there are windows in a lifetime when we are more susceptible to environmental exposures. The research also views the environment as inclusive of chemical, physical and socially constructed exposures that are incurred at home, in the community and at work. CBCPI will advance an ecological model of breast cancer and improved methodologies for incorporating all of the available science, such as from animal and other non-human “early warning systems” of evidence. Funded research will also explore how our food, water and consumer products contribute to risk overall and differentially among sub-populations. Finally, the environment and disparities research topics include concurrent exposure to psychosocial stress and environmental chemicals in animal and human models, and the role of discrimination, cultural and language barriers and immigration in breast cancer incidence.

6. Conclusion

In the 2013 *Ecology of Breast Cancer*, Ted Schettler proposed that the complexity of breast cancer can be understood as a “design problem” such that “we have collectively although unintentionally also designed current breast cancer patterns into the fabric of communities and society more generally” [19]. The CBCPI is an important effort to set a research agenda to help unleash the largely untapped potential of redesigning our society to prevent, rather than promote, the circumstances conducive to breast cancer. A major limitation of our efforts is that the research opportunities identified far exceed CBCRP’s funding capacity. Ultimately, it will be critical that other major funders increase support for research on breast cancer, the environment and prevention, and harness the resulting science for efforts to improve public policy if we are to succeed.

Conflict of interest

The authors declare that there are no conflicts of interest.

Transparency document

The [Transparency document](#) associated with this article can be found in the online version.

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expert assessment on post-menopausal breast cancer. Professor Deborah Cory-Slechta of the University of Rochester Medical Center conducted the expert assessment on experimental models of breast cancer and psychosocial stress. Dr. Tyler J.S. Smith and Dr. Keeve E. Nachman of Johns Hopkins Bloomberg School of Public Health and Johns Hopkins Center for a Livable Future, respectively, conducted the expert assessment of hormones in food. Yvonne Day was the graphic designer who crafted the figures and tables for this article. Finally, this work and all of the CBCRP’s efforts would not be possible without the on-going contribution of our vibrant community of stakeholders who ensure CBCRP’s research agenda meets the needs of the individuals, families and communities impacted by breast cancer. This work was supported by funds received by the University of California from the State of California to support the California Breast Cancer Research Program (grant number 16QB-8101).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.reprotox.2014.09.008>.

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