

# Maximizing the Impact of the California Breast Cancer Research Program: Studying Environmental Influences and Breast Cancer

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The California Breast Cancer Research Program commissioned this white paper in the summer of 2003 to help inform our tri-annual priority-setting process.

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# Overview

## **The importance of research on breast cancer and the environment**

Historical data, migrant studies, twin studies, and geographic patterns of breast cancer incidence around the world suggest that environmental factors play an important role in the etiology of breast cancer. In the United States, an increase in the incidence of breast cancer since the 1940s remains unexplained, and cannot be accounted for by increased detection or changing distributions of known risk factors. Various hypotheses have been advanced to explain these data, including aspects of modern lifestyle, pollution, and infectious agents. One would assume in the face of such a wealth of descriptive data that the environment and breast cancer would be a major focus of epidemiologic research. This has not been the case. Most epidemiologic studies of breast cancer focus on a narrow range of behaviors, such as smoking and alcohol, and ignore a broader spectrum of potential environmental risk factors. Recently, the focus of etiologic research has narrowed even further with an emphasis on breast cancer genetics, and investigators often ignore environmental exposures that interact with genes. The strongest rationale for studying environmental exposures is that many are preventable. Intervening on the basis of modifiable environmental exposures may offer our only hope for reducing the burden of breast cancer.

## **Benefits and limitations of genetic research**

Research in breast cancer genetics has yielded important information. Patterns of somatic genetic alteration and gene expression identify subtypes of breast cancer that appear to respond differently to chemotherapy, radiation, and other forms of treatment. These findings may revolutionize how we treat breast cancer. However, few attempts have been made to link patterns of somatic genetic alteration to etiology, to use information about what genes are mutated in breast tumors to identify the underlying causes of breast cancer. Cloning of the BRCA1 and BRCA2 genes was a tremendous advance, but so far, genetic testing benefits only a minority of patients with a strong family history. In the past five years, more common genetic polymorphisms, including single nucleotide polymorphisms, moved to the forefront of breast cancer research. Common genetic polymorphisms modulate response to diet, hormones, DNA damaging agents, oxidative stress, and other environmental factors. However, the majority of epidemiologic studies that incorporate these common genetic markers ignore the environment and assume that genes act alone.

## **Integrating genetic and environmental research**

Whole-genome association studies are planned that aim to build comprehensive multi-gene models for breast cancer. Such studies take full advantage of the wealth of information provided by the human genome. The goal is to identify each of the 30–40 inherited genetic variants that, in different combinations, act to determine a woman's risk of breast cancer. But these multi-gene models ignore environmental exposures, as well as interactions between genes and environment. In a very real sense, we may be missing the boat. Over sixty years of descriptive data tell us we need to look carefully at the environment, especially in areas where lifestyles and exposure histories vary across population subgroups. We need to make our investigations of environmental risk factors and breast

# Overview

cancer as far-reaching, comprehensive, and ambitious as studies of breast cancer genetics. In the age of discovery science, huge databases, and data mining, there is no reason that a net should be cast only for genes. Just as breast cancer genetics is now studied at many levels, including somatic alterations and inherited genetic variation, so the environment can be studied at many levels by evaluating individual and group level exposure to a wide variety of potential risk factors. Once we integrate comprehensive knowledge of genetics and environmental factors, we will have a much stronger handle on the causes of breast cancer. In areas such as California where environmental databases already exist and mechanisms exist for collecting additional data, studies of the environment can actually be done more quickly and cheaply than studies of genetics.

## **Proposal for a comprehensive investigation of breast cancer and the environment lead by the CBCRP**

The California Breast Cancer Research Program is in an ideal position to sponsor the first truly comprehensive research program aimed at studying breast cancer and the environment. The following document reviews environmental influences and breast cancer risk, identifies resources in the State of California that could be used to study the environment and breast cancer, and lists specific controversies and topics that could be topics for grants awarded by the CBCRP. A series of recommendations are made for future research. This list is not meant to be all-inclusive, but rather to provide examples of the types of studies that could be done. The advantages of a comprehensive approach to breast cancer and the environment sponsored by the CBCRP are that evaluation and funding would be regionally focused, would build on existing databases and research collaborations, and would capitalize on the rich diversity of the California population. With such a program, the CBCRP could make a major contribution toward addressing the many unanswered questions regarding breast cancer and the environment, and thereby have a huge impact on breast cancer research both within the state and beyond.

# Environmental influences and breast cancer

## a. Descriptive epidemiology

It is quite clear that environmental factors play an important role in the etiology of breast cancer. Incidence rates for breast cancer vary tremendously throughout the world (Henderson et al., 1996). The highest incidence rates are found in industrialized countries, including the US, Northern Europe, and Canada, while lower rates are found in Asia and Africa. Differences in incidence could be due to differences in screening and reporting, but comparisons of international breast cancer mortality rates show similar patterns. Mortality rates are based upon death certificates and do not depend upon cancer registries for data collection, and are not influenced as strongly by cancer screening as incidence rates. Some of the most compelling evidence for environmental factors comes from long-term comparisons of breast cancer incidence rates within the United States. Here, a long-term, “background” increase in breast cancer incidence since the 1940s remains largely unexplained, even after accounting for mammographic screening and trends in distributions of known breast cancer risk factors (Feuer, 1992). The increase in breast cancer incidence in the United States of about 1 percent per year for the past sixty years could be due to a variety of factors (Feuer et al., 1993; King & Schottenfeld, 1996), but one thing is quite clear: it cannot be ascribed to genetics alone.

Studies of women who migrate from Asia to the United States, in particular the Bay Area of Northern California, suggest that breast cancer rates rise to US levels soon after women migrate to the US (Thomas & Karagas, 1996). Migrant studies suggest that features of the physical environment, including early life experiences, play an important role in breast cancer risk. Even if genetic factors play a role in breast cancer risk among women of other countries, migrant studies suggest that these genetic factors must interact with environment factors in the host country. Twin studies estimate that the heritability of breast cancer is very low, about 27% (Lichtenstein, 2000). This does not mean that the environment alone is responsible for the remaining 73 percent of breast cancer, since gene-environment interactions could be involved. Nor does it mean that genes cause 27 percent of breast cancer, since twins also share environments. But it does mean that genes most certainly are not the only cause of breast cancer.

## b. Clues to environmental influences

The traditional view is that hormones cause breast cancer, except in rare cases where women in high-risk families inherit mutations in genes such as *BRCA1* or *BRCA2*. Recent evidence shows that this view is too narrow. A broader view of breast cancer causation is needed that takes environmental factors into account. But how do we define the environment?

### Defining “environment”

A conference on breast cancer and the environment convened by the National Breast Cancer Coalition in Washington DC in 1998 proposed a working definition of the “environment” to include “voluntary exposures as well as involuntary exposures, social class, and urban/rural differences, and exposures that occur outside the body as well as those that modify the internal milieu.” A summit on breast cancer and the environment held in Santa Cruz, California in 2002 defined the environment as “the totality of living and working conditions as well as the physical, biological, social, and cultural responses to those conditions.” The latter summit emphasized that “environmental exposures are often influenced by social, economic, and cultural factors such as employment, income, and housing” and include exposures related to occupation or residence, as well as industrial emissions, pollution, and hazardous chemicals. For the purposes of this paper, environment will be taken in the broadest sense, as proposed by these two conferences. Another way to categorize environmental factors in this context is “everything except for genes,” recognizing that genes and environment often interact.

### Definitions of causality

Epidemiologists define risk factors as exposures that are associated with an increase or decrease in the number of cases of illness in a population. The association may be direct (as in the case of cigarette smoking and lung cancer) or indirect (when an exposure such as age serves as a proxy for a more proximal risk factor). The association may be causal (true) or non-causal (due to chance or bias). Causal associations fall into several categories: the exposure may be a necessary cause (present in all cases of disease), sufficient cause (able to cause disease on its own), or a contributory cause (neither necessary nor sufficient, but present as one of many component causes in some but not all cases of the disease). Associa-



tions may also be classified as strong (e.g., risk ratios or odds ratios greater than four) or weak (risk ratios close to the null value of one). Most known risk factors for breast cancer are contributory causes, exposures with weak effects that are neither necessary nor sufficient for disease. Therefore, it should be no surprise that environmental risk factors for breast cancer, including any that are newly identified or under investigation, are likely to have very weak effects and act only in combination with other risk factors.

### **c. Hormonal risk factors**

The most widely recognized risk factors for breast cancer are female gender and increasing age. Women develop breast cancer at over one hundred times the rate as men, and rates increase dramatically as women get older. Classically, age and female gender serve as proxies for cumulative exposure to ovarian hormones. The mitogenic effects of estrogen combine with progesterone to increase proliferation of breast epithelial cells, increase the likelihood of mutation, and thereby lead to tumor formation (Pike et al., 1993). For most epidemiologists, in fact, female hormones are the main cause of breast cancer. Reproductive profiles, including age at menarche, age at menopause, parity, as well as obesity and height, are well-established risk factors and are presumed to be proxies for lifetime estrogen exposure. Epidemiologic studies consistently demonstrate a positive correlation between blood levels of estrogen and related metabolites and breast cancer risk later in life (Pike et al., 1993). For this reason, most epidemiologists would probably state that breast cancer is a “hormonal” cancer, and all or most risk factors for breast cancer operate by modulating levels of estrogen and progesterone, or related metabolites.

Under the hormonal theory of breast carcinogenesis, environmental exposures that occur outside the body contribute to increased breast cancer risk only by raising levels of estrogen-related metabolites, or act to mimic such metabolites within the body. Much research has been devoted to identifying environmental exposures such as xenoestrogens that may act in this manner. Promising work is being conducted in the area. However, a broader view of breast cancer causation is emerging that suggests that even hormonal-related exposures are more complex than we once thought. For example, alcohol consumption and postmenopausal hormone replacement therapy (HRT) show consistent associations with increased breast cancer risk, especially long-term

use, and until now both exposures fit well within the hormonal theory of causation. Both alcohol (by raising estrogen levels) and HRT (synthetic hormones) operate through hormone-mediated pathways. But recent evidence suggests that alcohol and HRT may also increase levels of oxidative stress. Estrogen metabolites are involved in redox cycling, and yield byproducts that can cause DNA damage and mutation (Zhu and Conney, 1998; Lin et al., 2003). Metabolites of alcohol (including aldehydes) cause oxidative DNA damage in a variety of organs.

Oxidative DNA damage due to estrogen exposure and estrogen metabolites may underlie many of the established hormonal risk factors for breast cancer (Zhu and Conney, 1998). In the past, the focus for investigation of environmental risk factors for breast cancer has often been on xenoestrogens and environmental pollutants or contaminants that may mimic estrogen. If the underlying mechanism for estrogen-mediated breast carcinogenesis is really oxidative stress, then the search for environmental risk factors should also consider chemicals that alter redox cycling and exposures that modulate levels of oxidative DNA damage, rather than just estrogen or estrogen-like compounds per se.

### **Limitations of the hormonal theory of breast carcinogenesis**

An unfortunate outgrowth of the hormonal theory of breast carcinogenesis is the assumption that *all* breast cancer risk factors are hormonal. Hormonal risk factors may represent component causes, neither necessary nor sufficient for breast cancer. Several hormonal risk factors for breast cancer, especially age at first birth, actually represent the degree of differentiation of breast tissue. In rats, later age at first full term pregnancy leads to increased susceptibility to a variety of environmental carcinogens. It may be that reproductive history and other hormonal risk factors for breast cancer merely set up a “fertile soil” for the effects of environmental exposures later in life. Thus, hormones may act in combination (or interact) with environmental exposures. In one simple model for carcinogenesis, environmental exposures cause mutations in DNA. These mutations become fixed and perpetuated in daughter cells by hormone-induced cellular proliferation.

Why do these theories matter? If interactions between hormones and environment are important, we will miss these effects if we estimate main effects for environmental factors while adjusting for hormonal risk factors

as potential confounders. Countless epidemiologic studies have “ruled out” associations for environmental exposures and breast cancer simply by adjusting away these effects, while ignoring the potential for interactions between the environment and “known” risk factors.

Endogenous hormone levels could represent intermediates, determined in large part by environmental exposures, especially those that act early in life. Onset of menarche and regular menstrual cycling may be influenced by diet, obesity, and possibly a variety of estrogenic exposures (including chemicals) in the environment. Not enough research has been done of how physical activity and chemical exposures influence age at menarche and maturation/differentiation of breast tissue in young women. Some epidemiologic studies estimate effects for environmental exposures after adjusting for hormone levels in blood. This approach is not valid if hormone levels are intervening variables between environmental exposures and disease, and will lead to invalid estimates of effect.

Thus, we can see how, rather than “explaining” breast cancer, hormonal theories for breast cancer may actually be pointing us towards whole new avenues of research. These new research areas include studying interactions with environmental exposures and investigating new biochemical pathways for breast carcinogenesis. Rather than “closing the book” on the etiology of breast cancer, the latest knowledge of how hormones might work opens the door to the investigation of new environmental risk factors for breast cancer. Most importantly, some of these new environmental risk factors may be modifiable.

#### **d. Environmental risk factors**

The strongest known environmental risk factor for breast cancer is exposure to ionizing radiation. A strong association has been observed between high dose exposure in atomic bomb survivors and persons undergoing prolonged radiation treatment. But few studies have been conducted of low dose occupational exposures or common medical procedures (Henderson et al., 1996). Women who underwent radiation treatment for Hodgkin’s disease and other cancers are at increased risk of breast cancer later in life. So are women who were treated with radiation for scoliosis, underwent repeated cardiac catheterizations, or underwent other diagnostic procedures. But at present it is not possible to

identify which women should avoid such procedures or undergo alternative treatments. The risk of breast cancer from nuclear power plants and other low-level sources of ionizing radiation has not been extensively studied, but is thought to be negligible. Nevertheless, considerable concern exists about such an association among many grassroots advocacy groups.

Despite scores of epidemiologic studies and decades of research, the association between tobacco smoke and breast cancer remains controversial (Laden and Hunter, 1998). Difficulties in measuring exposure, particularly passive exposure early in life, and disentangling the effects of the complex mixture of compounds within tobacco smoke are a few of the problems encountered. Cigarette smoke may increase breast cancer risk by raising levels of oxidative DNA damage. Exposure to ionizing radiation also increases levels of oxidative damage, so it is possible that hormones, alcohol, smoking, radiation, and many other environmental factors share oxidative damage and perhaps other biochemical pathways as common mechanisms of action in breast carcinogenesis.

A variety of factors have been identified as suspected environmental risk factors for breast cancer. These include: light at night (disruptions in melatonin secretion), hormone disruptors (including an extensive list of widespread compounds such as phthalates), environmental pollutants (hydrocarbons, organochlorines), and occupational exposures (chemical, radiation). The role of electromagnetic fields has been given less attention recently, with more emphasis on light at night as a source of melatonin disruption. Epidemiologic studies have shown fairly consistent associations between shift work and other sources of exposure to light at night and increased risk of breast cancer. It has been estimated that 20 percent or more of employed women in California may be exposed to light at night through shift work on jobs in health care, manufacturing, janitorial work, and transportation.

Infectious agents have long been suspected to play a role in breast cancer, including Epstein-Barr virus (EBV) and leukemia viruses of animals. Studies of EBV (Dr. Esther John) and Bovine Leukemia Virus (Dr. Gertrude Buehring) have been supported by the California Breast Cancer Research Program, and may yield important new information. Incidence rates of Hodgkin’s disease and breast cancer show strong correlations

in nationwide SEER data, which is of interest since delayed exposure to EBV is a risk factor for Hodgkin's disease. No studies have been done to examine potential geographic clusters of breast cancer and delayed EBV infection, but such studies would be interesting to study in relation to population density.

A number of lifestyle factors may affect breast cancer risk, including residence history and social class. To date, not enough research has been done in this area. Why do women of higher income and higher social class have higher incidence rates of breast cancer within the United States than women of lower social class? How much of the difference is due to early detection or increased reporting? How much is due to different life histories and environmental exposures? Mortality from breast cancer is higher in women of lower income and social class. How much of this difference is due to differences in access to health care? Studies of social class and breast cancer have been few and far between, and suffer from lack of data. Comprehensive databases are needed that collect information on race, social class, residence history, and access to care at the time of diagnosis (Krieger, 1990). Urban-rural differences are also important to study. Within the Carolina Breast Cancer Study, a population-based case-control study of breast cancer in African American and white women in North Carolina, researchers observed that women who lived or worked on farms and lived in rural areas had half the risk of breast cancer compared to women who lived in urban areas. The association persisted after adjusting for income and known breast cancer risk factors (Duell et al., 2001). Incidence rates of breast cancer are lower in rural areas than urban areas in many areas of the United States. How much of the urban-rural difference is due to lifestyle or other modifiable risk factors for breast cancer? How much is due to differences in reporting? These are important questions that could be readily addressed in California, an area with extensive urban, suburban, and rural populations. The gradient in population density within California makes it the ideal place to study urban-rural differences in breast cancer.

In order to answer these questions, complementary data collection would be needed. Residential histories and social class would need to be obtained with survey instruments that are developed to integrate with the California Cancer Registry database. Routine abstraction of medical records does not include such variables.

## **e. Why environmental factors for breast**

## **cancer are hard to study**

There are several reasons why it has been difficult to study breast cancer and the environment. A few possible explanations and potential solutions are listed below.

### **Lack of biologic knowledge**

The chief obstacle in studies of the environment and breast cancer factors has been lack of a firm biologic foundation. At present, for example, we do not know exactly how hormones increase risk of breast cancer, whether by stimulating cell proliferation, increasing levels of oxidative stress, or some other mechanism. This knowledge is important for understanding how hormones and the environment may interact. We do not know what mutations are necessary for breast cancers to develop, or what causes them. And we do not understand what changes in breast epithelial cells may be reversible, particularly later in life after damage has been done.

We do not know how protective factors work to lower the risk of breast cancer. Studies of physical activity and breast cancer need to be set on a firmer biologic foundation by investigating whether hormonal profiles, oxidative stress, the immune system, or other biologic pathways are involved. Do non-steroidal anti-inflammatory drugs lower risk of breast cancer by reducing oxidative stress or by enhancing apoptosis? What signaling cascades are important for breast cancer, especially non-hormonal pathways? Do some environmental exposures stimulate cell-signaling pathways to increase breast cancer risk? Do other exposures interfere with cell signaling to lower breast cancer risk? For example, recent epidemiologic studies suggest that insulin resistance may be a mechanism for breast carcinogenesis. Increased levels of insulin-like growth factor and related mitogens increase proliferative activity in the breast. Diet, physical activity, obesity, and a variety of other environmental exposures act to alter insulin-related biochemical pathways. Further study is needed to determine the extent to which insulin resistance and related biochemical pathways contribute to risk of breast cancer.

### **Misleading arguments on both sides**

There are two fallacious arguments surrounding the role of environmental risk factors for breast cancer. The first, a "pro-environment" stance, states that environmental factors must play a strong role in breast cancer etiology, because "the majority of breast cancer patients have no known risk factors." The second, an "anti-environment"



argument, proposes that environmental exposures are not worth studying because the effects are quite weak.

Contrary to the first argument, epidemiologic studies of breast cancer demonstrate that the majority of breast cancer cases do in fact have at least one “known” risk factor for breast cancer, defined by the list of hormone-related risk factors and family history (the “usual suspects”). The problem is that most unaffected women also have risk factors for breast cancer. For example, in the Carolina Breast Cancer Study (Newman et al., 1995; Millikan et al., 1995), 97 percent of cases and 96 percent of controls had one or more known hormone-related risk factors for breast cancer. The problem is not that traditional risk factors for breast cancer are rare, it is that they are *too common*: well-accepted risk factors for breast cancer do not distinguish well who will develop breast cancer and who will not. The effects of known risk factors, even in combination, are quite weak. This shortcoming can be seen in the Gail-model, which is based upon traditional risk factors for breast cancer. The model has only modest discriminatory power at the individual level, and cannot predict with high accuracy among individual women who will develop breast cancer and who will not (Rockhill et al., 2001).

Contrary to the second argument, one should not dismiss environmental risk factors for breast cancer because they are likely to have weak effects. Based on what we already know about traditional risk factors for breast cancer, one would predict that environmental factors will also have very weak effects, and represent contributory causes, neither necessary nor sufficient for breast cancer. Thirteen epidemiologic studies, including the Long Island Breast Cancer Study, have shown that risk of breast cancer is increased by roughly 50 percent in women with high exposure to polycyclic aromatic hydrocarbons. This increase in risk is twice that of hormone replacement therapy (HRT), which increases risk of breast cancer by 26 percent over a ten-year period, a level of risk sufficient to halt the HRT arm of the Women’s Health Study in July 2002. Postmenopausal obesity increases risk of breast cancer by 50 percent, and it is likely that intervention on the basis of diet and physical activity to reduce obesity would have a large impact on breast cancer occurrence in the United States. Environmental factors are not going to be the “smoking gun” for breast cancer. On the contrary, these exposures will usually demonstrate weak effects, similar to most known risk factors for breast cancer. Most probably,

environmental factors act in aggregate, rather than as independent exposures, in combination with hormonal factors at many different periods of a woman’s life over long periods of time.

### **Disease heterogeneity**

cDNA expression array data has shown that breast cancer is not one disease, but many diseases. Only some subtypes of breast cancer, for example, may be caused by exposure to tobacco smoke or other environmental factors. We should begin to think about sub-classifying breast cancer according to histology, patterns of somatic alterations, cDNA arrays and other characteristics in epidemiologic studies. Somatic genetic alterations in breast cancer have been well studied, but very little has been done to link these changes to specific etiologic agents. Aggregated data from large populations as well as data pooling will be needed for such investigations.

### **Latency and early life exposures**

Measuring early life exposure is a fundamental problem in the study of the environment and any type of cancer. Recognizing the need for such research, the National Institute of Child Health and Development recently launched a cohort study to investigate the role of early life exposures in risk of cancer and other health outcomes later in life. Similar studies have recently been funded as part of the NCI/NIEHS combined program on Centers for Breast Cancer and the Environment. Breast cancer is one of the main health outcomes of interest. One way that breast cancer susceptibility can be studied in younger women and girls is to study alternative health outcomes. Rather than breast cancer as the health outcome, intermediate health outcomes can be studied that are already known to increase risk of breast cancer later in life, for example, early age at onset of menarche.

### **Failure to address susceptibility**

Epidemiologists generally recognize that exposure does not cause disease by itself, but disease is caused by a combination of exposure and susceptibility. Susceptibility can come in many forms. Susceptibility to breast cancer is a function of age and stages of breast differentiation and development. Race, social class, and population density appear to influence susceptibility to breast cancer in ways that are not well understood. Many studies of the environment and breast cancer neglect to study exposure within this greater context, or focus on populations of women with similar income and social standing. The latter has decreased power to detect the effects of a variety of environmental exposures.

Currently, increased attention is being devoted to genetic or inherited susceptibility. The advent of new molecular techniques has brought numerous advances and will undoubtedly provide important opportunities for greater understanding of breast carcinogenesis. Genetic variation in susceptibility to the effects of environmental factors such as tobacco smoke may explain why only some women appear to be susceptible to these exposures. The breast itself has metabolic activity, and may activate as well as sequester a variety of environmental contaminants (Morris and Seifter, 1992). While pesticides, including organochlorines, and aromatic hydrocarbons in general do not appear to be strong influences on breast carcinogenesis, the jury is still out on a variety of chemical exposures. Some of these compounds undergo metabolism in the liver, lung, breast, and other tissues. Some act by damaging DNA. Genetic differences in carcinogen metabolism and DNA repair may help to sort out the association between many environmental exposures and breast cancer. Genetic markers need to be incorporated into epidemiologic studies of breast cancer before concluding that suspect chemicals play no role in etiology. For example, three epidemiologic studies have shown that the association of breast cancer and exposure to polychlorinated biphenyls is modified by inherited polymorphisms in cytochrome P450 genes. Most groups that fund breast cancer research list gene-environment interaction as a high priority. However most of the emphasis recently has been on genes, not the environment. Even studies of gene-environment interactions and smoking in breast cancer are often small and include only rudimentary exposure histories.

### **Need for improved exposure assessment**

The summit on breast cancer and the environment in Santa Cruz, California, in 2002 listed improved exposure assessment as its highest priority for future research into breast cancer and the environment. Better biomarkers are needed to identify exposure to chemicals, pollutants, and agents that modify cell signaling within breast tissue. When disease outcomes are measured close to the time of action of environmental exposures, power to detect effects is increased. Thus, biomarkers are needed for early disease within the breast that can be linked to etiology, not just for early detection and clinical intervention but also to better understand the causes of breast cancer. We need to develop improved biomarkers of exposure (e.g. assays for low-levels of chemical pollutants in blood and tissue) and biomarkers of early disease (e.g. alterations in cell signaling pathways, activation of

oncogenes, down-regulation of tumor suppressor genes) that can be linked to these exposures.

Candidate environmental exposures such as chemical pollutants also need to be studied at the aggregate or group level, not just at the individual level. Databases that include levels of environmental pollution could be linked to breast cancer incidence data from cancer registries. In this manner, regions with higher or lower breast cancer rates could be studied in relation to ground water contamination, pesticide and herbicide use, and levels of endocrine disruptors in water and soil. Studies on Long Island and Cape Cod have addressed some of these issues, and provide promising leads. But much of the environmental exposure information in these studies had to be collected *de novo*. In California, due to Proposition 65, records of pesticide use and other environmental exposures are routinely captured in publicly accessible databases and could be linked to incidence data from the California Cancer Registry. One issue in such studies is population migration, but obtaining residence histories for persons residing over long periods of time in California would overcome many of these problems. California is the only state with this level of environmental data, and mining it to understand the causes of breast cancer is critical.

# Resources in the State of California to study the environment and breast cancer

Resources exist in the State of California to conduct a comprehensive investigation of breast cancer and the environment. By combining these resources, California has an opportunity that no other state or country can match.

## a. Unique geography and demographics

California has a unique physical environment in which to study breast cancer. Differences in geography (including soils, groundwater aquifers, and other features) provide a rich testing ground for environmental theories about breast cancer. Additional features of interest include the wide diversity in income, social class, and culture; influx of immigrants from low incidence areas such as Asia, including 1st, 2nd and 3rd generation immigrants from Asia and Latin America; urban, suburban, and rural areas; racial and ethnic diversity.

## b. Unique databases

The presence of a statewide SEER-supported cancer registry ensures that high quality incidence data will be available. The California Cancer Registry was established in 1972 for the Los Angeles County region, and since 1988 includes the entire state. Even prior to SEER funding, the Registry received a “gold” rating, the highest level of certification for cancer registries. Reliable long-term estimates of cancer incidence, the ability to study *in situ* breast cancer and different histologic subtypes of breast cancer in large numbers, and the infrastructure to add new measures of social class and urban/rural status provide a strong foundation for breast cancer research.

Databases mandated by Proposition 65 that list pesticides and other pollutants are an important resource. The US EPA has estimated that 14.1 million persons nationwide routinely drink water contaminated with five or more herbicides. Ten percent of community water systems and 4 percent of rural wells in the US show persistently high levels of one or more pesticides or pesticide break down products. The fumigant DBCP is routinely found in groundwater in California, even though it was banned in 1979. These existing databases provide the ideal platform for future research studies. The databases could be readily supplemented through complementary

data collection. Survey sampling methods could be used to characterize census tracts according to socioeconomic status, access to care, occupation, water quality, and other factors at minimal cost.

## c. Research institutions and environment

The presence of several schools of public health, the strong resources of the State Health Department, and other groups have a long record of expertise in epidemiology and environmental sciences and engineering. Multi-center collaborations among these groups have been conducted in the past, and provide the basis for effective, efficient research studies in the future. Investigators with expertise in disease-mapping and cluster analysis, ecologic and other descriptive studies, and population-based epidemiologic studies are present in the state. Several institutions have long track records in the analysis of gene-environment interactions, and could be effective partners in studies that seek to determine the risk from low dose environmental exposures such as chemical pollution.

## d. Local cancer advocacy and grass roots environmental groups

The presence of strong environmental and cancer advocacy groups in California provides opportunities for partnerships that will strengthen breast cancer research. The summit on breast cancer and the environment held in Santa Cruz, California, in 2002 included representatives from several advocacy groups. The report from the summit includes specific recommendations for community based participatory research. One recommendation was that several types of communities be considered: geographic (e.g., persons living in an area with high rates of breast cancer), demographic (e.g. persons of similar social class), consumer-oriented (e.g. patients with similar barriers to quality health care), and issue-oriented (e.g. persons with a point view regarding pesticides as a cause of breast cancer). Each of these groups can make valuable contributions to the design and implementation of epidemiologic studies, most notably in the area of participant recruitment and retention (Plummer et al., 2002). The Office of the President of the University of California sponsors awards Com-

munity Research Collaboration grants. This program provides an ideal way to include community members in the research process, and has established technical assistance and outreach mechanisms to help such collaborations come about. Investigators in California who routinely work with advocacy groups include Margaret Wrench and Georgianna Farren at the University of California, San Francisco, and Rajiv Bhatia and Karen Goodson-Pierce in the San Francisco Department of Public Health.

# Issues and controversies in California that could be addressed by the CBCRP

## a. Supposed cancer clusters

Studies of breast cancer incidence show considerable variation within countries and within smaller geographic units, particularly in the United States. A suspected “cluster” of breast cancer has been identified in the northeastern United States (Kulldorf, 1997). More recent analyses suggest that “pockets” of increased breast cancer incidence are found in the western and mid-western United States, as well as the possibility of smaller “clusters” in Marin county and other regions of California. A major limitation of these studies is a failure to examine incidence rates in comparable geographic units. Historically, breast cancer incidence and mortality rates in California have been compared at the county level. Rates in small counties such as Marin are compared to rates in large counties such as Los Angeles. Residual heterogeneity and possible sub-county aggregation cannot be addressed in this manner. The comparability problem could be addressed by computing breast cancer incidence rates for census tracts and aggregating regions with comparable demographics. Incidence could then be compared in regions with comparable demographics, for example Marin County and Beverly Hills. Areas with high as well as low breast cancer incidence rates need to be studied, since low incidence areas might provide clues to identify protective factors.

Such studies would require applications of novel statistical methods, and need pilot testing and validation. Incidence rates could be aggregated according to the newest cluster methods, such as the “moving window” approach (Kulldorf, 1997). Bayes or semi-Bayes methods would need to be used to compute incidence rates in small geographic units, and would require development of new software applications. There are several reasons why this type of work is important: it would answer important questions for residents of high incidence areas, it would avoid unnecessary expenditure of time and money in regions where clusters do not actually exist, and it would lay an important foundation for monitoring breast cancer rates in the future.

## b. Reporting biases

According to the California State Cancer Registry, 40 percent of breast cancer cases are reported from hospitals without tumor boards. The advent of increased

SEER support will help to determine how much variation in cancer incidence rates in the state may be due to differences in reporting. Such differences are important to address when making comparisons of rates according to social class, and urban/rural status.

## c. Race, social class and breast cancer

Comparisons of breast cancer incidence and mortality rates in different racial and ethnic groups often fail to address differences in social class (Krieger et al., 1997; Faggiano, 1997). Information on residence histories and social class could be gathered from cancer patients in California and included in the Cancer Registry database. Patient residence history could be used to link cancer rates to census tract and group level information on income, employment, social class, and other risk factors for breast cancer.

A dramatic increase has occurred in the number of persons living in poverty in the United States. The US Census Bureau reported that the number of Americans living in poverty increased by 1.7 million in 2002, the second year in a row. The median family income declined for the second year in a row. The gap between the wealthiest and poorest individuals in the US has widened, and in California the gap is now the highest in the nation. It has become increasingly important to understand how income and social class differences influence risk of breast cancer and access to effective treatment.

## d. Distributions and determinants of age at menarche, age at menopause, and other reproductive risk factors for breast cancer

Survey methods could be used to gather information at the census tract level on traditional risk factors for breast cancer. This information could be used to determine whether such factors aggregate in specific geographic regions and population subgroups.

The information could also be used to adjust for confounding in ecologic studies of environmental exposures and breast cancer. For example, earlier age at menarche is an accepted risk factor for breast cancer. Average age at menarche appears to be decreasing among women in the US, especially in specific population subgroups defined by geography, race, and social class. Determinants



of age at menarche, attained height during adolescence, and obesity are some of the outcomes that need to be studied at the individual as well as the aggregate level. For example, one could study average ages at menarche across geographic regions (ecologic studies) and link this information to environmental databases. One could then determine whether average age at menarche was lower in regions with heavy use of pesticides or other sources of environmental contamination. In areas where correlations were observed at the group level, investigators could conduct investigations that gather individual level information (cross-sectional or case-control studies). Exposure histories in individual women could be further investigated, perhaps by including blood levels of persistent organochlorines and biomarkers of exposure to other environmental chemicals.

### **e. The effect of mammography on stage at diagnosis of breast cancer**

One goal of screening mammography is to decrease the incidence of late stage breast cancer. However, SEER data for the US and screening trials in Canada suggest that an increase in incidence of *in situ* breast cancer is not followed by a reduction in the incidence of late stage breast cancer. It is possible that such a reduction takes longer than ten to twenty years, but it is also possible that early detection finds many breast cancers that would never develop into life-threatening invasive cancer. If the latter is true, then considerable resources are being spent on mammography that could be more effectively used for other breast cancer-related activities. Analyses of long-term breast cancer incidence rates in California would address this issue. Such studies must take into account the prevalence of mammographic screening, since it is possible that women who are diagnosed with late stage breast cancer are the women who are not being screened. It is important to collect incidence data over longer time periods than recent clinical trials of screening mammography.

Differences in screening prevalence also need to be addressed in comparisons of breast cancer rates by social class and geography. Data on geographic differences present according to stage at diagnosis of breast cancer would be interesting. Specific studies could be funded to investigate potential explanations for such differences, including geographic and economic barriers to receiving health care.

### **f. Environmental contaminants and breast cancer risk**

A recent study showed that levels of bromine-based fire retardants are found at higher levels in breast milk from women in the San Francisco Bay Area than anywhere else in the world. The study was too small to address where in the Bay Area population and for whom these levels might be highest, and no correlations were made with environmental sampling to determine sources of exposure. No attempt was made to address risk of breast cancer from such exposure. Other potential breast carcinogens do not accumulate in the body, and thus cannot be studied at the individual level using blood or fat measurements. Group level data may be the only way to study such exposures. Information on environmental levels of these compounds could be studied using GIS and geo-coding and linked to breast cancer incidence rates or to existing case-control studies of breast cancer.

One example of such an approach is a recent study by Aschengrau et al. (2003). The investigators used residence histories and inspection of home piping systems to estimate exposure to perchloroethylene (PCE)-contaminated drinking water. Study participants with the highest PCE exposures had a small increase in risk of breast cancer. Ecologic studies of drinking water have linked increased breast cancer rates to higher levels of a variety of environmental pollutants. One strength of the Aschengrau et al. (2003) study was the fact that investigators collected individual level information on traditional breast cancer risk factors and combined this with ecologic level exposure measurement using geographic information system (GIS) mapping software and other techniques.

## Recommendations for future research

### Step One

As a first step, dozens of descriptive studies could be conducted at relatively little cost using data linkage. For example, recent reports of breast cancer clusters in California could be evaluated using incidence rates mapped to census tracts and other units smaller than the county level. In this manner, one could avoid invalid comparisons of small counties (e.g. Marin) with large, more heterogeneous counties (e.g. Los Angeles). New statistical applications, including Bayesian methods, need to be developed to make such comparisons, and could be developed under the sponsorship of the California Breast Cancer Research Program.

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### Step Two

As a second step, complementary data collection sponsored by the California Breast Cancer Research Program could be used to maximize the potential of existing infrastructures. For example, databases maintained by the California Cancer Registry could be supplemented with survey information. Residential history could be collected routinely on a subset of cancer patients, or even all patients with certain forms of cancer, and integrated with the Cancer Registry database. Existing databases containing information on pesticide use, water quality, and other environmental exposures could then be linked to Cancer Registry data to generate new hypotheses about potential etiologic agents. Survey sampling methods could be used to gather the information needed to examine correlations between breast cancer incidence and distributions of known breast cancer risk factors, screening, social class, and access to health care. Such investigations are necessary to address potential confounding variables in studies of the environment, as well as to identify inequalities in access to health care. Studies of migrant communities and cross-regional comparisons of breast cancer rates will further help to uncover modifiable risk factors that are amenable to population based interventions to reduce the burden of breast cancer in California.

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### Step Three

As a third step, researchers in academic institutions in California could be funded through the California Breast Cancer Research Program to conduct focused epidemiologic studies to better understand novel etiologic agents. Many of these institutions already have experience in epidemiologic studies and could be sponsored to expand the scope of existing studies or initiate new studies. Many investigators have already collected DNA from study participants and could be sponsored to study interactions between newly identified candidate environmental exposures and genetic susceptibility. Genetic markers may be quite useful in identifying low-dose environmental effects and helping to uncover biologic mechanisms, so genetics research and research on the environment can work hand in hand. Most agencies that fund breast cancer research list gene-environment interaction as a high priority. However, most of the emphasis and funding has focused on genes, not the environment. Better survey instruments, studies that link residential history to existing environmental databases, and new biomarkers of environmental exposure are areas that merit extensive research.

#### ::Examples::

Specific examples of the types of studies that could be performed are listed below. In these proposed studies, environmental factors are not studied in isolation but within a greater context that includes social class and urban rural differences at the macro level, and genetic susceptibility and biological mechanisms at the micro level. Only by integrating research across all of these areas, a feat that has never been previously accomplished or

proposed by any funding agency, is research on breast cancer and the environment likely to succeed.

#### a. Descriptive studies

Public health surveillance through improved monitoring of breast cancer rates was a primary recommendation of the summit on breast cancer and the environment held in Santa Cruz, California, in 2002. Studies are needed to develop methods for calculating breast cancer incidence

and mortality rates at the census tract and other sub-county levels. Newly developed Bayesian estimation procedures could be applied, such as those developed by Tom Mack at the University of Southern California. Newer cluster methods developed by Kuldorff (1997) and others could be used to identify regions with higher and lower breast cancer rates. Such analyses would need to take into account differences in known risk factors, screening, and population demographics. Once regions of interest were identified, ecologic studies linking cancer rates to environmental databases could be conducted.

Cancer rates also need to be studied over time among migrants. Periodic surveys of immigrants could provide clues regarding the role of reproductive patterns, diet, and physical activity.

### **b. Urban rural differences**

A comprehensive, statewide study could be conducted comparing breast cancer incidence rates in regions defined according to newly developed indices of urban/rural status. Urban Influence Codes (UICs) (Baer, 1997) were developed by the US Department of Agriculture as a county level measurement that captures adjacency to large metropolitan areas. Using UICs, rural areas are not categorized according to population density alone, but by proximity to urban areas. Rural Urban Commuting Area Codes (RUCACS) were developed by the US Census Bureau (Comartie 1996; University of Washington School of Medicine, 2003). RUCACS are used at the census tract level and categorize communities according to traffic flow where people commute for employment. They are especially useful where there are pockets of urbanization within non-metropolitan areas (so-called micropolitan areas) (Hewitt, 1992).

### **c. Studies of social class and traditional risk factors**

Ecologic studies could be performed linking incidence rates to distributions of known risk factors, screening practices, and social class. Group level proxies for physical activity (availability of bike trails, parks, etc.) could also be explored. Currently funded studies such as that of Margaret Wrensch at the University of California, San Francisco, examining risk factors for breast cancer in Marin County, including adolescent exposures, are particularly important. Several measures have been created and validated to capture information on social class that could be incorporated into cancer registry data collection (Krieger et al., 1997). Information on known

risk factors is also important when evaluating regional differences in breast cancer, and may make important contributions to areas where rates appear to be elevated (Robbins et al., 1997).

### **d. Studies of environmental contamination**

Once information is collected at the aggregate level on potential confounding variables, one could begin to explore the relationship between regional (group-level) environmental exposures and breast cancer. One could link residential history information to regional information regarding crop and pesticide use practices. For example, ecologic studies could be performed linking breast cancer incidence rates to Proposition 65-mandated reporting of pesticide use and related databases. Geo-coding and GIS methods could be used to link incidence rates to levels of environmental pollutants, toxins, and ambient levels of light at night. Residential history information or some proxy of migration frequency would need to be included. Analytic methods have been developed for measuring levels of endocrine-disrupting chemicals in ground water and other locations that could be used to characterize census tracts (Rudel et al. 1998).

One potential statistical technique that takes advantage of regional information on health outcomes is contextual analysis, in which group effects are estimated after controlling for individual-level covariates (Humphreys, 1991). Studies of pesticide exposure, for example, could be modeled at the group level using pesticide use databases and at the individual level using blood samples. One could collect residential history information (for example, for ten years prior to diagnosis of breast cancer), and link water quality, crop spraying, and other ecologic level information, while adjusting for individual level risk factors that are potential confounders as determined from questionnaires.

Surveys of wildlife, including reproductive problems, birth defects, and fetal malformations, could be used to characterize census tracts according to potential exposure to endocrine disruptors and other chemicals. Health outcomes in commercial and domestic animals might also prove useful in this regard. This information could be incorporated into ecologic studies of patterns of breast cancer incidence in women.

### **e. Incidence rates for subtypes of breast cancer**

Incidence rates for different stages of breast cancer, specific histologic subtypes of breast cancer (in particu-

lar, inflammatory breast cancer), and subtypes according to hormone receptor status could be analyzed. Subtypes of breast cancer may have distinct etiologies and show up in specific geographic patterns, or according to social class or other characteristics of breast cancer patients. Incidence rates and distributions for multiple primary cancers (breast as well as other types of cancer) could be evaluated.

### **f. Interdisciplinary investigations**

The summit on breast cancer and the environment held in Santa Cruz, California, in 2002 recommended that multi-disciplinary and inter-disciplinary approaches be used to study breast cancer and the environment. Toxicologists, epidemiologists, biologists, geneticists, social scientists, and others all need to be involved in studies where they act not as separate investigators, but as part of research teams. The interdisciplinary research team approach is the foundation for the proposed Centers for the Study of Breast Cancer and the Environment to be funded by the National Institute of Environmental Health Sciences.

#### **Exposure assessment**

One of the most important areas of investigation is improved exposure assessment. Direct measurements of persons (e.g., blood levels of compounds) and the environment (e.g. water sampling) need to be refined and correlated for a number of candidate compounds. But many chemical residues are non-persistent, and we need better ways to model exposure. Some of these exposures may leave traces in the body, measured as increased expression of specific genes in circulating lymphocytes, by modulation of single transduction and by changes in the immune system. Toxicologists working with epidemiologists could develop new biomarkers of exposure, as well as early disease, for studies of breast cancer and the environment.

#### **Gene-environment interaction**

It is important to collect more information on the environment while simultaneously investigating mechanisms of disease and susceptibility to exposure. One of the most promising areas of research is studies of gene-environment interaction. Such studies were recommended as a promising area of research into the role of cancer and the environment in a recent report by the Institute of Medicine. To further such investigations in an efficient and timely fashion, it would be useful to provide supplemental funding for investigators with existing epidemiologic studies that collected DNA

samples. Studies of gene-environment interaction would be an efficient use of resources, since only funds for genotyping would need to be provided. However, one needs to think beyond the paradigm of genes involved in hormone metabolism. Candidate genes include variants involved in DNA repair, oxidative stress, and carcinogen metabolism.

Few studies have focused on mutations in P53 and other somatic alterations in breast tumors. It would make sense, when trying to understand etiology, to look first at breast tumors and discern whether patterns of somatic alterations provide clues to etiology. Mutations in P53 and other genes can be classified according to frequency, location, and type of base change (transition, transversion, deletion, etc.), and correlations with exposure histories conducted (Conway, 2002). Novel studies using new technologies for somatic changes could also be funded. For example, comparisons of cDNA expression array profiles for cancers that appear to occur in space-time clusters. Do such tumors share patterns of somatic alteration, suggesting a common etiology?

#### **Augmenting existing epidemiologic studies**

The CBCRP could fund studies to expand the environmental portion of existing epidemiologic studies. If study participants have previously collected residence histories, this information can be geocoded and linked to environmental databases funded by the CBCRP. Study participants who provided residential histories could then be categorized according to potential for exposure to water contaminants and a variety of environmental exposures. This information could be studied in conjunction with previously collected information on reproductive histories and other traditional risk factors for breast cancer.

### **g. Breast biology and breast development**

Until more is known about normal breast development and breast biology, studies of environmental risk factors for breast cancer rest on a weak foundation. Both the Institute of Medicine report (2002) and the NCI Progress Review Group on Breast Cancer (1998) listed breast biology and breast development as important areas for future research. The NCI/NIEHS funded Centers for Breast Cancer and the Environment include development of animal models for breast development and susceptibility, and will examine the effects of chemical

carcinogens and endocrine disruptors on breast biology. But more studies are needed of breast metabolism in humans, including the distribution and metabolism of environmental chemicals in breast tissue. Studies such as that of Peggy Reynolds at the California Department of Health Services and Vicki Davis at Cedars-Sinai of xenoestrogens in breast tissue should be encouraged, and could be expanded to understand how these compounds affect breast development. The previously mentioned studies of EBV and BLV and breast cancer will also yield important information with regard to breast biology.



## Conclusions

Over sixty years of data exist to support a role for environmental factors in the etiology of breast cancer. Most of the evidence is circumstantial. Research to date has been limited and suffers from lack of a coherent conceptual framework and access to adequate databases. The CBCRP has an opportunity to remedy the situation. California represents the ideal location for conducting a comprehensive evaluation of the environment and breast cancer. With its diversity of populations and physical environment, extensive environmental databases and infrastructure for collecting new data, California may be the only place where such a comprehensive investigation could be done.

A series of steps were proposed to initiate a research program in breast cancer and the environment sponsored by the CBCRP. Beginning with previously collected information, new statistical methods could be used to calculate incidence and mortality rates for breast cancer within smaller geographic units, thereby providing a clearer window on variation across the state. Existing databases could be augmented through complementary data collection: information on residence history, social class, and access to health care represent important potential additions to the California Cancer Registry. Patients in the Registry as well as participants in epidemiologic studies could be linked through residence history to a variety of environmental exposures through geo-coding. Much of the environmental exposure information needed for such investigations is already collected routinely under public mandate and could easily be supplemented in areas where breast cancer incidence is highest. Interdisciplinary investigations could build upon these databases to develop new biomarkers, examine novel biochemical pathways for breast development, identify markers of genetic susceptibility to environmental exposures, and study environmental factors that act during critical windows of susceptibility in a woman's lifetime.

Why should the CBCRP sponsor such an ambitious research program when there are other research priorities? Environmental exposures are likely to be weak, contributory causes of breast cancer, neither necessary nor sufficient for disease. Other priorities would seem to be more pressing: the development of new therapeutic drugs, novel methods for early detection, and addressing

inequalities in health care. In fact, the proposed research program addresses each of these areas, and would provide information that is needed *before* such investigations can proceed. Environmental factors will tell us a great deal about the biochemical pathways that lead to breast carcinogenesis, including aberrant cell signaling, elevation of oxidative stress, and modulation of estrogen metabolism, and this information will have important applications to treating and preventing breast cancer. At present, we do not know the extent to which current methods of breast cancer screening are successful, and this can only come by examining long-term trends in stage at diagnosis of breast cancer and identifying subgroups of women for whom screening has not been offered or followed through with effective treatment. Inequalities in health care have to first be understood before they can be addressed. Unfortunately, the extent to which geographic, economic, and social barriers exist to effective, high quality treatment for breast cancer has not been well studied.

Why should such a program be attempted in a time of limited funding? A CBCRP program on breast cancer and the environment would be an effective use of funds. At present, citizens living in regions with high rates of breast cancer often lobby separately for funding. Several studies of breast cancer have been conducted in very small geographic areas in California, and none have provided definitive results. An environmental research program sponsored by CBCRP would provide a coherent research program and infrastructure to follow up on these small studies with more definitive investigations. Such a program would help to avoid misuse of resources and help lay to rest clusters that represent false alarms. Anxiety over potential breast cancer clusters and persistent fears in the public about the role of pesticides, ionizing radiation, and other modifiable breast cancer risk factors need to be addressed in a comprehensive, interdisciplinary manner. To do otherwise would be irresponsible.

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