# Department of Health and Human Services
# Office on Women's Health
# Workshop on Breast Cancer and the Environment

**June 26, 2003**
**Washington, DC**

# Final Report

# Introduction

On June 26, 2003, the Office on Women's Health in the U.S. Department of Health and Human Services hosted a Workshop on Breast Cancer and the Environment. More than 40 researchers and advocates who are experts in the field attended this day-long workshop. Participants discussed recent findings and generated ideas on how to prioritize and implement research recommendations that have emerged from:

- The Long Island Breast Cancer Study,
- The Northeast and Mid-Atlantic Study,
- The Cape Cod Breast Cancer and the Environment Study,
- The Marin County Studies,
- The International Summit on Breast Cancer and the Environment,
- The Technical Workshop on Human Milk Surveillance and Research for Environmental Chemicals in the United States, and
- The Breast Cancer Clusters Workshop.

The overall goal of the workshop was to develop a framework in which the National Centers of Excellence in Women's Health can collaborate with researchers and advocates to study the relationship between breast cancer and the environment.

# Background

**Research in High-Rate Areas:**
Breast cancer incidence and mortality rates in certain geographic regions of the United States, such as the Northeast, and in certain smaller localities, such as Marin County, California and Cape Cod, Massachusetts, have consistently been higher than in other areas of the United States. In response to community concerns, several research investigations have been conducted to determine whether specific environmental exposures may be linked to breast cancer risk in areas with higher than average rates of breast cancer. These investigations include the Long Island Breast Cancer Study Project (LIBCSP) and the Northeast and Mid-Atlantic Study (NE/MA), both of which were mandated and funded by the federal government. In addition, several other studies are being conducted to examine factors that may be responsible for increasing breast cancer risk in Marin County, California and in Cape Cod, Massachusetts. These studies were originally funded in part by the California and Massachusetts state governments, respectively. Community members and breast cancer advocates have been involved, to varying degrees, in the design and the oversight of all four research endeavors.

The LIBCSP consists of twelve on-going studies that are designed to investigate the potential link between environmental factors and breast cancer in Suffolk, Nassau, and Schoharie Counties, New York, and in Tolland County, Connecticut. The largest of the twelve studies, the Breast Cancer and the Environment on Long Island study, is a population-based, case-control study. A total of 3064 women living in Nassau and Suffolk counties were enrolled in the study between 1996 and 1997. Data from the study did not show an association between breast cancer risk and levels of PCBs and DDE, two organochlorine compounds, in the blood of adult women (1). However, data from the same case-control study suggested that exposure to polycyclic aromatic hydrocarbons (PAHs) in adult women may be moderately associated with breast cancer risk (2). Women with detectable blood levels of PAH-DNA adducts had a 1.35 relative risk of breast cancer when compared to women with undetectable levels of adducts. This risk increase was statistically significant (95% CI, 1.01-1.81). No dose-response pattern was observed. Another LIBCSP study, the Electromagnetic Fields (EMF) and Breast Cancer on Long Island study, found no association between EMF and breast cancer (3).

The NE/MA included six concurrent case-control studies that were designed to examine the link between breast cancer and environmental factors in 10 Northeastern and Mid-Atlantic states. Five of these studies examined blood levels of DDT/DDE and PCBs; none found that organochlorine compounds were associated with increased breast cancer risk (4-8). A combined analysis of the five studies looked for possible interactions between the organochlorine compounds and several known breast cancer risk factors, including age, menopausal status, use of hormone replacement therapy, body mass index (BMI), and parity (9). Findings from the analysis were negative for all subgroups of women except for women in the middle tertile of BMI. Among these women, DDE was associated with an increase in breast cancer risk; however, there was no such association among women in the lowest or the highest tertiles of BMI.

Several of the individual studies from the NE/MA found statistically significant associations between breast cancer risk and environmental factors other than organochlorines, including consumption of dietary lignans; working on rotating night shifts; lactation; and blood serum levels of β-carotene, lycopene, lutein, and total carotene (10-13). In addition, some of the studies found interactions between environmental factors and certain genetic polymorphisms that mediate the metabolism of these factors in the body. For example, one study found that women who started smoking before age 18 had an elevated risk of breast cancer that was statistically significant only if they had a polymorphism in the CYP1A1 gene (14). Other gene/environment interactions were found between:

- serum levels of PCBs and CYP1A1 polymorphisms (15, 16);
- dietary lignan consumption and CYP17 polymorphisms (10);
- fruits, vegetable, α-tocopherol, and ascorbic acid consumption and MnSOD polymorphisms (17); and
- alcohol and ADH3 polymorphisms (18).

For a full list of the positive findings from the NE/MA, see Appendix A. These findings are very interesting and warrant further study.

In Marin County, California, several on-going research endeavors are underway to investigate factors that may be associated with breast cancer risk. One of these studies, the Adolescent Risk Factors Study (ARFS), is a population-based, case-control study that enrolled a total of 571 women from 1997-1999. The main purpose of this study is to investigate the relationship between breast cancer and relatively unexplored adolescent risk factors among women in Marin County.

Initial results from the ARFS have confirmed that several known risk factors, including menopausal status, alcohol consumption, and BMI, are linked to breast cancer risk in this population (19). Strangely, no association was found between breast cancer risk and family history, parity, HRT use, or age at menarche; however, the confidence intervals around each OR were wide. Even more puzzling was the finding that oral contraceptive use was associated with a statistically significant reduction in breast cancer risk. There was no association between breast cancer risk and years lived in Marin County or years lived in Marin County before age 21. However, there was a statistically significant increased risk among women under the age of 50 who had been born in the Northeast or Great Lakes areas of the United States. Finally, breast cancer risk was independently associated with radiation treatment in women under age 50 and with smoking for more than 28.5 pack-years.

The somewhat confusing findings of this study highlight a drawback to conducting studies in small, high-risk areas; they tend to be homogeneous with regard to demographics as well as distributions of risk factors. On the other hand, because such areas will tend to be homogeneous with regard to know breast cancer risk factors, they may be useful for investigations of environmental exposures; participants in such areas

will tend to be "pre-matched" on known breast cancer risk factors, yet may vary in terms of localized environmental exposures.

The Cape Cod study was designed to be conducted in two phases. Phase I, which is complete, aimed to identify regional environmental factors using novel methods. These activities revealed that several suspect exposures, including radon, EMF, and air pollution, are not more common on Cape Cod than in areas with lower rates of breast cancer (20). During Phase I, researchers developed a geographic information system (GIS) that includes data on water quality and pesticide use that occurred decades in the past. They also developed novel methods for measuring estrogenic activity in air, dust and water.

Phase II of the Cape Cod study, which is currently underway, includes a population-based, case-control study of 2,100 women living in Cape Cod. Several reports analyzing data from this study are expected to be published this year. Results from a related study of Cape Cod women found that women who were exposed to high amounts of perchloroethylene in their drinking water had an elevated risk of breast cancer (21). Women were exposed to this chemical, which is used in dry cleaning, when it leached from the vinyl lining of water distribution pipes from the late 1960s through the early 1980s. Women may also be exposed to perchloroethylene by wearing clothes that have been cleaned using the chemical.

Thus far, the results of the research investigations conducted in high-rate areas have helped to clarify the relationship between several environmental exposures and breast cancer risk. These studies have also helped to identify new avenues for future research endeavors. Despite the progress that has been made, the relationship between the environment and breast cancer risk, and the factors that contribute to breast cancer risk in high-rate areas, remain elusive.

One important limiting factor that has slowed progress in this field of research is the fact that there are thousands of environmental exposures and most of these are very difficult to assess in humans. Thus, only a small proportion of exposures have been studied in humans to date. In addition, humans are exposed to multiple factors over a long period of time, which makes it challenging to both measure and link individual exposures to health outcomes. Moreover, in retrospective studies, it is particularly difficult to assess exposures that occurred at the time of breast cancer initiation, perhaps decades in the past. For example, in the LIBCSP and in four of the NE/MA studies, researchers measured blood levels of organochlorines, which may only reflect adult exposures to these compounds. It may be more important to examine exposures that occurred during key periods of a woman's life, such as adolescent, childhood, and prenatal exposures.

Exposure assessment and study design issues are just some of the many factors that make identifying casual relationships between environmental factors and breast cancer challenging. Further progress in this area of research will likely require novel approaches and a strategic, organized effort.

**Previous Consensus Building Meetings:**
During the past few years, numerous consensus building meetings have been convened in order to develop recommendations and strategies for advancing the study of breast cancer and the environment. The following three meetings were some of the most innovative and successful:

1. The Breast Cancer Clusters Workshop was hosted in December 1998 by the Office on Women's Health in the Department of Health and Human Services. This meeting brought together experts from both the scientific and advocacy communities to develop a framework for investigating high-rate areas and for determining possible environmental causes of breast cancer (22).
2. The Technical Workshop on Human Milk Surveillance and Research for Environmental Chemicals in the United States was held in February 2002 at the Milton S. Hershey Medical Center, Pennsylvania State University College of Medicine. An expert panel, comprised of more than 30 participants, came together to define the components of well-conducted human milk surveillance and research studies, reach conclusions, and enumerate research needs (23).
3. The International Summit on Breast Cancer and the Environment was funded by the Centers for Disease Control and Prevention (CDC) and hosted by the University of California, Berkeley in May 2002. This meeting brought together almost 100 participants representing a wide variety of perspectives, including researchers, advocates, health professionals and policymakers to develop recommendations for research, education, communications, and policy (24).

**Research Recommendations:**
Many research recommendations emerged from the major studies conducted in high-rate areas and from the three consensus building meetings described above. These recommendations address four subtopics: 1) cancer registries; 2) breast milk research; 3) risk factors and exposures; and 4) research methods and design. A full list of the recommendations in each subgroup can be found in Appendix B. Many of these recommendations could potentially be carried out by a network of academic health centers called the National Centers of Excellence in Women's Health (CoEs). In particular, the CoE's have the capacity to:

- Create investigator networks and new strategies to collaborate in jointly ascertaining study populations and establishing shared infrastructure and specimen repositories.
- Set up multi-disciplinary collaborations by integrating the research efforts of epidemiologists, geneticists, molecular and cell biologists, endocrinologists, environmental scientists, and biostatisticians.
- Design and implement large, prospective, multi-center epidemiological studies.
- Examine ethnically diverse groups with differing breast cancer rates
- Include and involve breast cancer advocates and representatives from the community at all stages of the research process, from the design stage through the final analysis and report.

The Office on Women's Health (OWH) in the US Department of Health and Human Services believes that the CoEs are well positioned to advance the study of breast cancer and the environment.

**The National Centers of Excellence in Women's Health (CoEs):**
The CoEs are sponsored by the OWH and serve as demonstration models for the nation to provide innovative, comprehensive, multidisciplinary, and integrated health care systems for women. There are nineteen CoEs based in academic health centers across the United States; Appendix C lists each center and its location. The CoEs provide for the special needs of women, including the underserved and minorities, by integrating:

- state-of-the-art comprehensive and integrated health care services,
- multidisciplinary research,
- public and professional education, training, and materials,
- community linkages for health services and programs, and
- leadership positions for women in academic medicine.

The unique infrastructure of the CoEs and their strong links to communities could enable them to implement important research recommendations to advance the study of breast cancer and the environment. Breast cancer research is a priority for the current administration and for the OWH. (To find out more about the CoEs, please visit their main website at http://www.4woman.gov/CoE/).

**Workshop Goals and Structure:**
The OWH brought together 40 experts in the field of breast cancer and the environment for a one-day workshop on June 26, 2003. The purpose of the workshop was to 1) prioritize and refine the research recommendations in Appendix B; 2) generate specific research ideas and action items for each recommendation; and 3) develop a framework in which the CoEs can collaborate with researchers and advocates to implement the some of the recommendations. Workshop participants included representatives involved in the major breast cancer studies in high risk areas as well as other knowledgeable breast cancer advocates and researchers in the field. The meeting was also attended by representatives from several CoEs, including the CoEs at the University of Illinois at Chicago, the University of California at Los Angeles, Boston University Medical Center, the University of Pittsburgh, the University of Wisconsin at Madison, and MCP Hahnemann University (doing business as Drexel University). A full list of workshop participants can be found in Appendix D.

The first half of the workshop consisted of several short presentations made by workshop participants who were invited to speak. The purpose of these presentations was to update all participants on the state-of-the-science and to provide a springboard for subsequent discussion. The presentation topics included:

- current activities and research capacities of the CoEs,
- research funding from the Department of Defense Breast Cancer Research Program,

- research funding from the National Institute of Environmental Health Sciences (NIEHS), including the new Breast Cancer and the Environment Research Centers
- findings and recommendations from studies in high-rate areas and previous consensus building meetings,
- human milk surveillance and research,
- exposure assessment and measurement issues, and
- perspectives of the breast cancer activist/advocate community

The second half of the workshop was devoted to free flowing brainstorming and discussion sessions involving all of the participants. Three sessions focused on the first three subgroups of research recommendations in Appendix B: cancer registries, breast milk research, and risk factors and exposures. The workshop hosts asked a few specific questions; however, for the most part, participants were given leeway to direct the course of the conversation. The participants were asked to consider the purpose of the workshop and to be as specific as possible with their ideas on how to prioritize and narrow the recommendations.

During these three sessions, the participants also addressed many issues related to research methods and design. Towards the end of the meeting, participants spent time individually considering the recommendations for risk factors and exposures. Each person was asked to rank these recommendations in order of importance. The individual rankings were collected and compiled.

# Workshop Results

**Participant Comments:**
The outline below details the wealth of specific research ideas, action items, and recommendations that individual participants came up with during the three discussion and brainstorming sessions of the workshop. Although each session was largely unstructured, certain themes arose and some consensus was reached around these themes. Specifically, there were several important questions that were collectively answered by the group by the end of each session. These questions and the group's answers are arranged in an outline format below. Each bullet point is a comment that was made by at least one of the workshop participants.

I. Cancer Registries

a. What are some efforts that are currently underway to improve U.S. cancer registries and what are some examples of good databases?

- Many of the state cancer registries in the U.S. are not optimal. The CDC has administered the National Program of Cancer Registries (NPCR) since 1994. This program is currently helping states and U.S. territories to improve their cancer registries.
- The CDC wants each state to have a cancer control plan for upgrading their registries. Only those registries that meet certain criteria will get funding from CDC. Because of this effort, cancer registries may improve.
- California has a registry that seems to be working – it is a very valuable statewide resource. Los Angeles has a rapid reporting system that collects data on most diagnoses within three weeks. Both of these registries are part of the SEER registry.

b. What changes/improvements could be made to U.S. registries, databases, and medical records to facilitate better research on breast cancer and the environment?

- States could provide more adequate funding, mandate improvements and give incentives to the registries, hospitals, and/or physicians.
- The information that is abstracted from medical records can be problematic because medical records are often incomplete or incorrect. The data need to be cleaner and easier to collect. This is something that could be worked on through special hospital committees, such as the JCHO.
- Medical records need to more accurately capture people's occupations.
- Information is often not collected/reported in a timely manner. We need to have more rapid reporting and surveillance.
- Cancer data could be linked to other useful data, such as occupational data. However, there are minimal relevant data sets within the states.
- There are various impediments for researchers who want access to registry data. For example, the kinds of data that are necessary for many studies are

difficult to obtain due to the HIPAA rules. In addition, it is difficult to get the raw data, such as street addresses, that is necessary to study clusters. The purpose of the registry is to advance research; therefore, the data should be readily available to researchers.

- Registries need to be more cost effective.
- Currently, you can only get information on where the person lived when they received the diagnosis. You cannot find out where they lived when they were exposed. It would be helpful if registries collected more of the kind of data that would be useful to researchers, such as long-term residential data.
- Cancer registries could include information on known breast cancer risk factors so that researchers can identify areas where known risk factors account for less than the expected amount of cases – then these become areas of interest for investigation of unknown risk factors. We could develop a standard reporting form for known risk factors. Investigators who obtain contact information from the registry would be asked to use this standard form and report back the information to the registry to be included in the registry. CoEs could partner with registries to develop this auxiliary data compilation.
- The quality of birth certificates varies immensely from place to place. Birth certificates could be made more accurate and include more information. Birth certificate data could also be linked with cancer registry data. Some special study issues would need to be resolved such as identifying women who changed their names after marriage.

c. What are some of the limitations of using registries for breast cancer research?

- Colon cancer studies in the 1980's linked the disease outcome to occupational data. (25, 26). As a result of these studies, we now know that physical activity decreases the likelihood of getting colon cancer. However, this method may not move the field of breast cancer along because, often, what women do for work does not represent their various exposures. For example, a rural housewife and an urban housewife have very different exposures.
- Improving registries may not be cost-effective and may not get us where we want to be.
- Using registry data based on occupation and residence may not be the best route because ecological data will not give answers to new questions and will not lead us in new directions that need to be taken. There is too much expectation from ecological studies and there is a limit to what we can learn from linking to tumor registries to other registries.
- We need to put money into complex studies. Targeted, well-designed, analytic studies such as case-control and cohort studies allow the right questions to be asked and more accurately assess the relevant exposure.

d. What are some ways that registries might be useful in breast cancer research?

- Populations are constantly in motion. Thus, a database of residential history would help answer the question of whether or not women lived in a particular

area long enough to be exposed and whether or not they lived there during the appropriate period of exposure.
- Registries have good potential and can be used for hypothesis generation.
- Cancer registries could be used to determine if there are any correlations among clusters of different cancers. In addition, they could also be used to determine if there are clusters of cancers in children that predate the breast cancer clusters.
- We could use registries to identify special populations, geographic areas, or occupational groups that might be important and/or interesting to study. For instance, we could identify and study populations with high breast cancer incidence rates that have low rates of known breast cancer risk factors. We could also identify and study populations with low breast cancer incidence rates that have high rates of known breast cancer risk factors.
- We could put resources into creating an incidence map of the U.S. so we would know the areas to study.

e. How can we design a study to follow high-risk and low-risk populations in parallel?

- We first have to define what high risk and low risk mean. We also have to determine what would be a significant enough difference between the two to make an impact.
- We could use the top quartile vs. the bottom quartile of incidence.
- We could study two towns near each other: one town with a high incidence of breast cancer and low prevalence of risk factors and one town with a low incidence of breast cancer and high prevalence of risk factors.
- It is difficult to know where people have lived all their lives or where they have lived the longest. We would need to use people who had lived in their homes for an extended period of time. For example, the Long Island study on EMF enrolled women who had lived in their homes for 15 years or more.
- We could use the CoEs to collect additional data in the identified areas.
- Pools of money could be put together from multi-centers and agencies to do one large, well-designed study.

f. Would it make sense to conduct a large, longitudinal cohort study (e.g. Framingham study) for breast cancer and how should we design such a study?

- We would need a 40-year study of 100,000 to 200,000 children or adolescent girls designed to learn everything about everyone. The duration and size of the study may make it onerous and costly.
- We could develop a stronger collaborative relationship with basic scientists to identify early markers for breast cancer such as a protein or a protein expression pattern. The intermediate marker must first be adequately tested with long-term follow-up so that we know whether it accurately predicts breast cancer. Then, these markers could be used as surrogate endpoints in breast cancer studies so that we could design shorter studies. Alternatively,

we could identify a group of women who already have the markers and are therefore at high risk for breast cancer. Then we could follow this group of high-risk women. The duration of such a study can be shorter because more breast cancer cases will be diagnosed in a shorter period of time.

- Use the large cohort of 150,000 postmenopausal women from the Women's Health Initiative to do ancillary studies. We could use this cohort or other established cohorts to conduct nested case-control studies.
- We could do a series of coordinated case-control studies in several places instead of cohort studies. The CoEs are ideal settings for such an endeavor.
- We could study women who are at high risk based on known risk factors, such as nulliparous women with early menarche. We could follow them across the menopausal period (from age 30-50). This study would not require very long follow-up, and we could get answers about at least one period of life.
- We could use The National Children's Health Study and add breast cancer as a study outcome. This study is currently in the planning process. It will enroll 100,000 families – enrolled preconception or *in utero* – and follow them through age 21. If it is successful and could get more funding, follow-up could last longer.
- Perhaps we can learn from the way Europeans, particularly the Scandinavians, collect their data. Whole life epidemiology is reported very well in Europe. There is a cohort of 120,000 Swedish women who gave blood at pregnancy.
- In the U.S., there are standard times during pregnancy that specimens are collected, but many specimens are simply thrown out. We could use these specimens to study a large number of individuals.

II. Breast Milk Research

a. What biomonitoring efforts are currently underway?

- There are several trusts, including the Pew Charitable Trusts and the Trust for America's Health, that advocate for national biomonitoring and health tracking in the U.S.
- Some states have passed health-tracking legislation. Maryland just got funds to set up a small study of pesticides in urine.
- CDC is giving money to states for biomonitoring purposes. Biomonitoring can include utilizing any biological matrix, including breast milk. States are currently submitting grant proposals and funding will be awarded based on certain criteria. Thus far, the CDC has not allocated the funds.

b. What are some of the difficulties with obtaining breast milk samples?

- In California, it is difficult to obtain samples from milk banks. Some breastfeeding advocates in this state are not supportive of biomonitoring breast milk. They believe that such efforts will discourage women from breastfeeding because women will fear that breast milk is contaminated.

- It is unclear whether it is more or less difficult to get women to donate breast milk than blood samples. Pilot studies are needed to answer this question. Some women may be highly motivated to donate breast milk if they are exposed to something that may be harmful (e.g. antibiotics during pregnancy). However, if women have not been obviously exposed to something, they may feel that is too bothersome to donate their breast milk for a study.
- Not all U.S. milk banks collect information on donors and donors may not be representative of the general population of pregnant women. Thus, milk bank samples may be unsuitable for some research studies.

c. What are some successful ways to obtain breast milk samples?

- There are 6 milk banks nationwide that collect donated milk daily to give to infants requiring breast milk. OWH can help researchers gain access to these banks.
- Participation rates will increase if you go into the community and attempt to know and understand the women. Researchers have used this method to successfully collect hundreds of milk specimens from poor Latino farmers. They held focus groups first and found out the best way to approach the women and urge them to participate in the project.
- It is easier now than it was in the past to get women to donate milk. Many women are pumping milk now to go back to work.
- We could train La Leche League members to be recruiters in their communities.
- We could increase the funding for existing cohort studies and support the collection and analysis of breast milk as part of these studies. For instance, The National Children's Health Study is planning to collect breast milk from mothers.

d. What are some of the limitations of banking breast milk and of using breast milk for breast cancer research?

- Collecting and monitoring breast milk might not be the most cost effective research endeavor because breast milk may not be the most appropriate matrix to study.
- Many chemicals are not detectable in breast milk. Breast milk is high in lipids; thus, lipophilic compounds (e.g. dioxins, PCBs, organochlorine pesticides, brominated flame retardants, etc.) are routinely found in breast milk. However, many non-persistent compounds exist only transiently in breast milk and are not easily detected or measured.
- Breast milk may not be useful for answering important questions about breast cancer. For instance, if we want to look at exposures that occur during various stages in a woman's life cycle, breast milk will not be useful.
- There is a high correlation between the chemicals found in umbilical cord blood and the chemicals found in breast milk. It may be easier to get cord blood than breast milk because the woman is not involved in collecting the

cord blood. However, cord blood is very low in lipids relative to maternal blood and it can only be collected at one point in time, which is a disadvantage.

- National biomonitoring programs are important, but we first need to determine the most appropriate matrix to study and the most appropriate communities to target. Researchers at the EPA and the CDC, including two of the workshop participants (S. Fenton and L. Needham, respectively), are currently conducting a joint study to compare contaminants in milk to contaminants in other body fluids.
- We need to decide what the driving hypotheses are and choose the exposures first. Then we should choose the matricies and populations that are most appropriate to answering the hypotheses.
- Despite the fact that research has shown that breastfed infants have better health outcomes than formula-fed infants, efforts to bank and analyze breast milk may deter women from breastfeeding because they may fear that their milk is contaminated.
- Breast milk research would exclude nulliparous and non-lactating women, groups that are at higher risk for breast cancer.

e. What are some reasons to use breast milk as opposed to other matrices?

- We need to involve the communities and consider their interests and values. Breast milk research is important to communities. This kind of research will have more resonance, more buy-in and less resistance because communities will feel like they have some control over the type of research.
- Collecting and analyzing breast milk may not only be useful for determining whether certain environmental exposures are related to breast cancer; it could also answer another important research question: Is breast milk contaminated? Currently, we have very little data to answer this question. We need to increase our knowledge in this area so that we can confidently assuage women's fears about breastfeeding
- Breast milk flows through the breast ducts which are where most breast cancers originate.
- Milk has a higher fat content than other body fluids and is therefore a reservoir for lipophilic environmental contaminants.

f. What are some ways that breast milk might be useful in breast cancer research?

- We could study the cytology of cells collected from breast milk in relation to subsequent risk of breast cancer.
- We could use breast milk to better understand the small sub-group of breast cancer cases that occur during pregnancy.
- Breast milk can be used as a way to find out which exposures are getting into the breast ducts and which stay mostly in the blood. Specifically, we could determine the level of exposure in the blood and the level of exposure in the milk and calculate a ratio.

- We are persistently exposed to certain chemicals in our daily lives (e.g. perfumes, hair products, etc.) that may not be persistent in bodies. Phthalates and other chemicals in personal care products are in breast milk. We can use breast milk to screen for these chemicals in order to find out what our breast tissue is exposed to and what we are passing on in our milk. This information may give us new hypotheses and lead us to study novel exposures.
- We could use breast milk as a measure of relative community exposure, provided the women are selected on specific criteria. The World Health Organization (WHO) has created databases of women from Europe and New Zealand for this purpose. We could do the same thing in the U.S. By studying women aged 20-30 years, we can determine community exposures that occurred during the last 20 to 30 years. It could lead to ecological studies that compare exposures across communities and breast cancer rates.
- Lactation is associated with a decrease in breast cancer risk. Women who lactate for long periods of time or who breast-feed multiple children have the largest decrease in risk. We need to expand our knowledge base in this area. Is it because lactating cells become differentiated and do not replicate? Do the receptor populations in the breast change? Or is it because women who lactate are getting rid of chemicals that build up over time? We can use breast milk to help answer these questions.
- We can examine the risk of breast cancer associated with being breastfed as a child versus being formula fed.

g. Why should we create a biomonitoring program for breast milk specimens?

- We need to start banking samples that can be used for research in the future. There are more than 85,000 synthetic chemicals used in the manufacturing industry, but we have cancer information on not more than 1,000. The European Union is developing a new system for determining toxicology and carcinogenicity of high production synthetic chemicals (Reach Program), so we may start seeing more information on which industrial chemicals are carcinogens. In order to study these chemicals and find biomarkers for them, it will be necessary to have banks of several different types of historical samples (e.g. milk, urine, blood, etc.).
- We may need to do "fishing expeditions" (data mining) because the field is at an early point. We may need to go backwards -- first get the samples and then do analyses to see what chemicals are in there.
- We need to get baseline data for body burdens of chemicals, and breast milk is an easy way to start. It would be useful to see what contaminants are in breast milk and how their concentrations change over time.

III. Risk Factors and Exposures

a. Should we continue to study organochlorines and breast cancer risk and what kinds of studies do we need in this area?

- We should study pesticides that are endocrine disruptors.
- Some organochlorines had been studied extensively and some have received too much attention, but there are many others that have not been adequately studied and need to be examined. For example, the herbicide atrazine is hormonally active, but studies linking atrazine exposure to breast, ovarian, and other cancers in humans are limited (27, 28).
- Atrazine exposure causes mammary tumors in Sprague-Dawley rats. However, the mode of action for tumorgenesis in these rats does not pertain to humans (29).
- Atrazine is difficult to measure in the population due to its rapid degradation; it gets into the body, is metabolized, and gets out quickly.
- Triazines in general have not been well studied. Atrazine is the most widely used triazine, but there are other chlorotriazines and metabolites that are biologically active.

b. What other synthetic chemicals should we be studying?

- Phthalates and polybrominated diphenyl ethers (PBDEs) may be important to study. They are persistent chemicals and hormonally active, but we do not yet know if they are carcinogens in humans.
- Internal combustion exhaust chemicals such as polycyclic aromatic hydrocarbons (PAHs) have not been looked at closely enough.
- Perfluorooctanesulfonate (PFOS) and perfluorooctanoic acid (PFOA) are both very persistent and long-lasting compounds. PFOS is a breakdown product of Scotchguard, which is produced by 3M. The company has ceased production of the product. PFOA is involved in the production of Teflon, a product that is still being made by Dupont.
- Estradiol has been found in the water supply. It is possible that our excretion of HRT and OC is contaminating water. We should study this further.

c. With the large number of synthetic chemicals in the environment, how do we determine which compounds to study first?

- The National Toxicology Program has identified 42 chemicals that are mammary carcinogens. Two journal publications list each mammary carcinogen identified by the NTP as well as its species, sex, and mutagenicity (30, 31). Most of the chemicals have not been looked at in depth in epidemiologic studies. Some are used in occupational settings, and some have been phased out. We could start studying the chemicals on this list.
- Look at the US Geological Survey. It has data on both surface and ground water contaminants that will reveal which chemicals are water soluble. We should also look at breakdown products in addition to parent compounds because many breakdown products have greater biologic activity and/or half-lives than the parent compounds. Metolachlor and alachlor are examples of parent compounds that have breakdown products that we should study.

- Since breast cancer rates have been increasing, we could start with a list of chemicals whose levels have been increasing in the environment. Then we could see if there is plausibility or a mechanism for how the exposure could lead to breast cancer. We could also see if there are any life-style changes that have been occurring in the population that would increase certain exposures. Using these approaches, we could rank or pick out the most important chemicals to study.
- Start with estrogenic or anti-androgenic chemicals.
- We can find an intermediate marker of breast cancer development, and we could conduct a short study to screen numerous chemicals. We would identify those chemicals that cause the intermediate marker and then study them further with a larger, longer and more expensive study that uses breast cancer as endpoint.
- We could generate hypotheses by comparing the incidence of breast cancer in women to the incidence in men. If an area has elevated incidence in both male and female breast cancer, than the cause may be something other than reproductive factors.

d. Should we focus on individual compounds or should we study combinations of multiple compounds?

- There was a consensus at the Danish and Tulane University endocrine disruption meetings that the additive effects of multiple chemicals are more important to study than the effects of individual chemicals. Some groups have conducted bioassays in cells comparing individual chemicals with mixtures of several chemicals at low levels. The individual chemicals had no effect on the cells but the mixtures did. Humans may be exposed to 50 chemicals at low levels that are each only weakly estrogenic. Collectively, they may have an impact.
- We should study families of genotoxic chemicals together with families of susceptibility factors that affect the exposures. Statistical models can help deal with the multitude of data. Pattern recognition and multiple exposure modeling analysis methods are emerging and will get better with time. They have the capability of giving important results.
- One of the workshop participants (S. Fenton) had conducted research in which atrazine and its metabolites were combined to evaluate their effect on puberty and breast development (unpublished results). Once results were obtained there was a need to evaluate the individual components responsible for the effect not seen with the parent compound alone. Future research should examine single compounds *as well as* several mixed together. Modeling could be done with data from animals.
- It is important to understand the mechanism of action of the effects of individual chemicals. However, in reality, we are all exposed to multiple things over a long period of time. We need to develop technologies to help us understand what humans are exposed to, and we need to find out their combined effect on humans.

- We should look for a biologic intermediate or function that captures the effects of mixtures of exposures.

e. What are some examples of useful intermediate markers and what are their strengths?

- Mammographic density is an example of a good intermediate marker. It is one of the strongest predictors of breast cancer; women with very dense breasts have a 7-fold increased risk. The CoEs could conduct a study that uses this marker because they have mammographic facilities and can recruit women from the community.
- Studies are currently looking at mammographic density as a marker and many large clinical trials already use density as an endpoint. Some researchers believe that a volumetric density measure is the most important, and this type of measurement can not be accomplished using regular flat plate mammograms. Optical means of measuring density or magnetic resonance (MR) must be used. MR is considered superior to radiation. The technology will improve greatly in the future.
- One important marker is elevated estrogen level.
- Cytologic changes in breast cells could be used as an intermediate marker. We could extract ductal cells from women's breasts at multiple points in time using ductal lavage and then see if there is change over time in amount of atypical hyperplasia.
- Genotypic or proteomic changes are even better markers than phenotypic changes because they have the potential to be more specific and they can be observed at an earlier point in time. The Food and Drug Administration is testing these types of markers for ovarian cancer. We are about 18 to 24 months behind for breast cancer. Resources are being poured into this research, including funding from the Department of Defense and the National Cancer Institute.
- Proteomic changes may be more important than genomic changes. Just one protein found in blood or urine might be a sufficient marker.

f. What are limitations of these intermediate markers?

- Both mammographic density and estrogen level changes are difficult to observe in pre-menopausal women.
- Mammographic density and cytology of lavaged cells have poor specificity. In addition, when changes in these markers are detected, the cells may already have committed to a malignancy.
- There is no research to date that has answered the question of whether, in fact, reducing mammographic density reduces breast cancer risk.
- Genomic and proteomic markers have not been fully tested and are not available yet. These technologies have to go through the pilot stages in order to get to the point where we can use them in environmental research. Everyone supports this type of research, but we are not there yet.

- Tools for analyzing genomic and proteomic markers are not at a high through-put capacity. There are very few places that can process the large number of samples needed for a study of environmental exposures. This is a piece of infrastructure that needs to be funded.
- Any intermediate marker that we develop must first be adequately tested with long-term follow-up so that we know whether it accurately predicts breast cancer.
- There are ethical issues to consider when conducting a study using intermediate markers as an endpoint. What do you offer or say to women who develop the marker? The CoEs can do a huge part in education and outreach for women so that they understand the complexity and implications of this research.

g. What exposures are important to study besides synthetic chemicals?

- We should examine exposures that have been shown in some studies to reduce risk. Examples include smoking, dioxin, and soy products. While studies of these three exposures and breast cancer risk have had inconsistent results, some studies have shown a reduction in risk.
- Viruses, autoimmune system and inflammatory responses should be studied in connection to breast cancer.
- It is important to look at radiation use in medicine, particularly in young women. We should also study CT Scan use in children.
- Personal radiation use histories may be important to study. It is also important to develop ways to measure the amount of exposure to the breast. Perhaps the National Children's Health Study can document over time the amount of radiation the participants receive.
- We should study diet and define it broadly to include contaminants in food, fat intake, caloric intake, and energy balance. Food is an extremely complicated matrix with multiple exposures. We might also want to look at the effects of microwaving plastics.
- Obesity is important to study and it is a topic in which the CoEs are already interested; some are currently conducting studies of diet and exercise. Community-based centers are well suited to address this topic. Many children in the U.S. are obese, and obesity is associated with earlier age at menarche (32). Evidence suggests that weight gain in young adults affects breast cancer risk (33) but we do not know the effects of obesity on children. We could support incorporation of hypotheses covering these important gaps in knowledge that are currently pending within the National Children's Health Study.
- Since environmental exposures may be promoters rather than initiators, we need to study their effect on survival, tumor progression and metastasis rather than incidence. It is not clear that sufficient animal models have been developed to look at chemicals that promote cancer; more investigation is needed.

**Ranking Risk Factors and Exposures:**
After the brainstorming and discussion sessions ended, participants were asked to prioritize the list of recommendations on risk factors and exposures in Appendix B. They were asked to rank the recommendations from 1 to 11, with a ranking of 1 signifying the most important recommendation on the list and a ranking of 11 signifying the least important recommendation on the list. Thirty of the participants completed this task.

The table in Appendix E presents the compiled results for all participants. Several participants gave more than one recommendation the same ranking. In addition, several participants noted that obesity should be added to the recommendation on diet and several participants noted that viruses, autoimmune system, and inflammatory responses should be added to the recommendation on Epstein-Barr virus. These additions are reflected in Appendix E.

Each cell in the table contains a tally of the number of participants that gave each recommendation a particular ranking. For example, the first cell of the table shows nine tally marks. This means that nine participants gave a ranking of 1 to the recommendation to study known and unknown carcinogens. The number of tallies in each cell was multiplied by the rank, and the resulting number was listed in each cell below the tallies. For example, the second cell in the first row shows that seven participants gave a ranking of 2 to the recommendation to study known and unknown carcinogens. Thus, the number fourteen (7 X 2) is listed below the tally marks. These numbers were summed for each recommendation to determine the total ranking. Finally, the recommendations were given final rankings of 1 through 11 based on their total ranking. For example, the recommendation with the lowest total ranking was collectively considered to be the most important and given a final ranking of 1. The recommendation with the highest total ranking was collectively considered to be the least important and given a final ranking of 11. The final rankings for each recommendation are listed in both the last column of the table and below the table in Appendix E.

The three most importantly ranked recommendations, in order of importance, were 1) study suspected and known carcinogens, including pesticides, that have not yet been examined in relation to breast cancer risk (e.g. atrazine), 2) investigate synergistic effects between multiple exposures, and 3) study diet, particularly obesity and harmful contaminants in food, and breast cancer risk. The three least importantly ranked recommendations, in order of ascending importance, were 1) determine how the estrogen receptor status of tumors is related to risk factors for breast cancer; 2) study cigarette smoke, particularly passive exposure, and breast cancer risk; and 3) study the relationship between exposure to viruses, autoimmune system, and inflammatory responses and breast cancer risk. These results do not mean that the participants felt that the recommendations were unimportant--just that other recommendations should be addressed and funded first.

In addition to examining the collective final rankings, it is also interesting to note the results for each individual ranking. The recommendation that received the most rankings of 1 was to study suspected and known carcinogens, including pesticides, that have not yet been examined in relation to breast cancer risk (e.g. atrazine). Three

recommendations tied for receiving the second most rankings of 1. Each of the following recommendations received a ranking of 1 from five different participants 1) study traditional risk factors in light of environmental contaminants, including environmental hormones; 2) investigate synergistic effects between multiple exposures; and 3) study the relationship between breast developmental stages and breast cancer. These results are somewhat different than expected considering the final ranking results.

# Conclusions

**Synthesis of Workshop Results:**
Participants at the Office on Women's Health Workshop on Breast Cancer and the Environment generated a multitude of specific research action items and recommendations, which have been described in the above sections. There were some action items and recommendations that stood out for one or more of the following reasons: they were discussed more extensively than others, they were agreed upon by the majority of participants, and/or they are well-suited for the CoEs to address. These recommendations and action items have been synthesized and summarized in the list below.

1) Design studies to include women from two types of contrasting populations--a population with high rates of breast cancer, but low rates of known risk factors, and a population with low rates of breast cancer, but high rates of known risk factors. These populations may not necessarily be geographically defined. The CoEs could conduct such studies because they have access to varied populations of women across the U.S.

2) Databases that collect residential history and cancer incidence are important for generating hypotheses and for identifying appropriate study populations. Resources should be devoted to making these databases more accurate, complete and accessible for research purposes. Databases of women's occupations are of limited use and may not be cost-effective.

3) Fund ancillary studies and/or nested case-control studies to add on to the Women's Health Initiative and the National Children's Health Study.

4) A series of coordinated case-control studies conducted by the CoEs would be an adequate design for future research.

5) The creation of a national biomonitoring program is important. Preliminary research must be conducted to determine which matrices are the most appropriate and easiest to collect and bank. Umbilical cord blood, breast milk, urine, and blood are the most likely candidates. However, banking breast milk would enable many unique and important questions to be answered. For instance, we could examine whether breast milk contaminants are harmful to babies and which chemicals are getting into the breast. The CoEs could conduct pilot studies to answer some of these questions.

6) Future studies should examine the effects of mixtures of multiple chemicals in addition to single chemicals. New animal models need to be developed for this purpose.

7) Studies should focus on examining suspected and known carcinogens, including pesticides, that have not yet been examined in relation to breast cancer risk. Studies should also examine the link between breast cancer risk and diet, including obesity and harmful contaminants.

8) The list of suspected and potential carcinogens must be prioritized using a combination of strategies that may include using data from the National Toxicology Program and the US Geological Survey. Another promising strategy would be to conduct small studies that use an intermediate marker of breast cancer development as the endpoint. Numerous chemicals can be screened this way. Those chemicals that cause the intermediate marker would be examined further in the context of a larger case-control or cohort study that uses breast cancer as endpoint.

9) Breast density may be an ideal intermediate marker for breast cancer because it is a strong predictor of breast cancer. The CoEs could conduct studies that use breast density as an endpoint because they have mammographic and magnetic resonance facilities. Cytologic changes, such as the development of atypical hyperplasia, could also be used as an intermediate marker. Ductal lavage is a tool that can be used at the CoEs to measure this marker.

**Next Steps:**
This report will be circulated to the CoEs, and they will be asked to identify the recommendations and action items that they are most interested in and able to address. Conference calls will be set up between representatives from each CoE and those workshop participants who are interested in the items cited by the CoE. This report will also be circulated among officials in HHS who are involved in this area of research. Finally, OWH will follow-up on the recommendations that pertain to the National Children's Health Study and the Women's Health Initiative.

# References


1. Gammon MD, Wolff MS, Neugut AI, et al. Environmental toxins and breast cancer on Long Island. II. Organochlorine compound levels in blood. *Cancer Epidemiol Biomarkers Prev* 2002;11(8):686-97.
2. Gammon MD, Santella RM, Neugut AI, et al. Environmental toxins and breast cancer on Long Island. I. Polycyclic aromatic hydrocarbon DNA adducts. *Cancer Epidemiol Biomarkers Prev* 2002;11(8):677-85.
3. Schoenfeld ER, O'Leary ES, Henderson K et al. Electromagnetic fields and breast cancer on Long Island: a case-control study. *Am J Epidemiol* 2003;158(1):47-58.
4. Moysich KB, Ambrosone CB, Vena JE, et al. Environmental organochlorine exposure and postmenopausal breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 1998;7(3):181-8.
5. Helzlsouer KJ, Alberg AJ, Huang HY, et al. Serum concentrations of organochlorine compounds and the subsequent development of breast cancer. *Cancer Epidemiol Biomarkers Prev* 1999;8(6):525-32.
6. Hunter DJ, Hankinson SE, Laden F, et al. Plasma organochlorine levels and the risk of breast cancer. *N Engl J Med* 1997;337(18):1253-8.
7. Wolff MS, Zeleniuch-Jacquotte A, Dubin N, Toniolo P. Risk of breast cancer and organochlorine exposure. *Cancer Epidemiol Biomarkers Prev* 2000;9(3):271-7.
8. Zheng T, Holford TR, Mayne ST, et al. Risk of female breast cancer associated with serum polychlorinated biphenyls and 1,1-dichloro-2,2'-bis(p-chlorophenyl)ethylene. *Cancer Epidemiol Biomarkers Prev* 2000;9(2):167-74.
9. Laden F, Collman G, Iwamoto K, et al. 1,1-Dichloro-2,2-bis(p-chlorophenyl) ethylene and polychlorinated biphenyls and breast cancer: combined analysis of five U.S. studies. *J Natl Cancer Inst* 2001;93(10):768-76.
10. McCann SE, Moysich KB, Freudenheim JL, et al. The risk of breast cancer associated with dietary lignans differs by CYP17 genotype in women. *J Nutr* 2002;132(10):3036-41.
11. Schernhammer ES, Laden F, Speizer FE, et al. Rotating night shifts and risk of breast cancer in women participating in the Nurses' Health Study. *Journal of the National Cancer Institute* 2001;93(20):1563-68.
12. Zheng T, Holford TR, Mayne ST, et al. Lactation and breast cancer risk: A case-control study in Connecticut. *Br J Cancer* 2001;84(11):1472-6.
13. Sato R, Helzlsouer KJ, Alberg AJ, et al. Prospective study of carotenoids, tocopherols, and retinoid concentrations and the risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2002;11(5):451-7.
14. Ishibe N, Hankinson SE, Colditz GA, et al. Cigarette smoking, cytochrome P450 1Al polymorphisms, and breast cancer risk in the Nurses' Health Study. *Cancer Res* 1998;58:667-671.
15. Moysich KB, Shields PG, Freudenheim JL, et al. Polychlorinated biphenyls, cytochrome P4501A1 polymorphism, and postmenopausal breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 1999;8:41-44.
16. Laden F, Ishibe N, Hankinson SE, et al. Polychlorinated biphenyls, cytochrome P450 1A1, and breast cancer risk in the Nurses' Health Study. *Cancer Epidemiol Biomarkers Prev* 2002;11:1560-5.

17. Ambrosone CB, Freudenheim JL, Thompson PA, et al. Manganese superoxide dismutase (MnSOD) genetic polymorphisms, dietary antioxidants, and risk of breast cancer. *Cancer Res* 1999;59:602-606.
18. Freudenheim JL, Ambrosone CB, Moysich KB, et al. Alcohol dehydrogenase 3 genotype modification of the association of alcohol consumption with breast cancer risk. *Cancer Causes Control* 1999;10:369-377.
19. Wrensch M, Chew T, Farren G, et al. Risk factors for breast cancer in a population with high incidence rates. Breast Cancer Research 2003;5(4):R88-R102.
20. Silent Spring Institute. The Cape Cod Breast Cancer and Environment Study: Results of the First Three Years of Study. Newton, MA: Silent Spring Institute. 1998.
21. Aschengrau A, Rogers S, Ozonoff D. Perchloroethylene-contaminated drinking water and the risk of breast cancer: additional results from Cape Cod, Massachusetts, USA. *Environ Health Perspect* 2003;111(2):167-73.
22. Haynes S, Steingraber S, Balaban B, et al. Investigating breast cancer clusters. (unpublished).
23. Berlin CM Jr, LaKind JS, Sonawane BR, et al. Conclusions, research needs, and recommendations of the expert panel: technical workshop on human milk surveillance and research for environmental chemicals in the United States. J Toxicol Environ Health A. 2002;65(22):1929-35.
24. International Summit on Breast Cancer and the Environment: Research Needs. May 22 – 25, 2002. Chaminade, Santa Cruz, California. Online at http://socrates.berkeley.edu/~jmm716/BC%20and%20Environment%20Summit%20Final%20Report.pdf
25. Garabrant DH, Peters JM, Mack TM, Bernstein L. Job activity and colon cancer risk. *Am J Epidemiol* 1984;119(6):1005-14.
26. Vena JE, Graham S, Zielezny M, et al. Lifetime occupational exercise and colon cancer. Am J Epidemiol 1985;122(3):357-65.
27. Hopenhayn-Rich C, Stump ML, Browning SR. Regional assessment of atrazine exposure and incidence of breast and ovarian cancers in Kentucky. *Arch Environ Contam Toxicol* 2002;42(1):127-36.
28. Sathiakumar N, Delzell E. A review of epidemiologic studies of triazine herbicides and cancer. *Crit Rev Toxicol* 1997;27(6):599-612.
29. Eldridge JC, Wetzel LT, Stevens JT, Simpkins JW et al. The mammary tumor response in triazine-treated female rats: a threshold-mediated interaction with strain and species-specific reproductive senescence. *Steroids* 1999;64(9):672-8.
30. Bennett LM, Davis BJ. Identification of mammary carcinogens in rodent bioassays. *Environ Mol Mutagen* 2002;39(2-3):150-7.
31. Dunnick JK, Elwell MR, Huff J, Barrett JC. Chemically induced mammary gland cancer in the National Toxicology Program's carcinogenesis bioassay. *Carcinogenesis* 1995;16(2):173-9.
32. Slyper AH. Childhood obesity, adipose tissue distribution, and the pediatric practitioner. Pediatrics 1998;102(1):e4.
33. Stoll BA. Teenage obesity in relation to breast cancer risk. *Int J Obes Relat Metab Disord* 1998;22(11):1035-40.

# Appendix A: Positive Findings from the Northeast and Mid-Atlantic Study (NE/MA)

The following tables list publications that report at least one statistically significant (or borderline significant) association between an environmental factor and breast cancer risk. Studies are not included if the NE/MA combined analysis examined the positive association and failed to confirm it.

I. Environmental and Genetic Determinants of Breast Cancer
U01 CA/ES62995
Principal Investigator: Jo L. Freudenheim, PhD

| Study | Risk Factor(s) | OR (95% CI) |
|---|---|---|
| Ambrosone et al., 1995 | • CYP1A1-exon 7 polymorphism<br>• Light smoking and CYP1A1-exon 7 polymorphism | • 1.61 (0.94-2.75)<br>• 5.22 (1.16-23.56) |
| Ambrosone et al., 1996 | • Current smoking and NAT2 polymorphism in postmenopausal women<br>• Smoking in distant past and NAT2 polymorphism in postmenopausal women | • 4.4 (1.3-14.8)<br>• 3.9 (1.4-10.8) |
| Shields, et al., 1996 | • Smoking and CYP2E1 polymorphism in premenopausal women | • 11.09 (1.51-81.41) |
| Moysich et al., 1998 | • Less chlorinated PCB serum levels in postmenopausal women<br>• Mirex serum levels in parous women who never lactated | • 1.66 (1.07-2.88)<br>• 2.42 (0.98-4.32) |
| Moysich et al., 1999 | • PCB serum levels above median and CYP1A1-exon 7 polymorphism in postmenopausal women | • 2.93 (1.17-7.36) |
| Ambrosone et al., 1999 | • MnSOD polymorphism in premenopausal women<br>• MnSOD polymorphism in postmenopausal women<br>• Low consumption of fruits, vegetables and MnSOD polymorphism in premenopausal women<br>• Low consumption of ascorbic acid and MnSOD polymorphism in premenopausal women<br>• Low consumption of α-tocopherol and MnSOD polymorphism in premenopausal women | • 4.3 (1.7-10.8)<br>• 1.8 (0.9-3.6)<br>• 6.0 (2.0-18.2)<br>• 7.7 (2.5-23.9)<br>• 5.0 (1.7-14.4) |

| | | |
|---|---|---|
| Freudenheim et al., 1999 | • $ADH_3$ polymorphism in premenopausal women<br>• Alcohol consumption in premenopausal women<br>• Alcohol consumption and $ADH_3$ polymorphism in premenopausal women<br>• Alcohol consumption and $ADH_3$ polymorphism in postmenopausal women | • 2.3 (1.2-4.3)<br>• 1.6 (0.9-2.6)<br>• 3.6 (1.5-8.8)<br>• 1.2 (1.1-2.2) |
| McCann et al., 2002 | • High consumption of dietary ligands in premenopausal women<br>• High consumption of dietary ligands in postmenopausal women<br>• High consumption of dietary ligands and CYP17 polymorphism in premenopausal women | • 0.49 (0.32-0.75)<br>• 0.72 (0.51-1.02)<br>• 0.12 (0.03-0.50) |

II. Environmental Risk Factors and Breast Cancer in the Nurses' Health Study
U01 CA/ES62984
Principal Investigator: David J. Hunter, MBBS, ScD

| **Study** | **Risk Factor(s)** | **OR (95% CI)** |
|---|---|---|
| Hunter et al., 1997 | • Current smoking and NAT2 polymorphism<br>• Current smoking and NAT2 poly-morphism in postmenopausal women<br>• Smoking 1-5 years before first pregnancy in parous women<br>• Smoking 5 or more years before first pregnancy in parous women | • 1.4 (0.7-2.6)<br>• 1.8 (0.9-3.6)<br>• 1.9 (1.2-2.8)<br>• 1.1 (0.8-1.6) |
| Ishibe et al., 1998 | • Smoking before age 18 and CYP1A1-MspI polymorphism<br>• Smoking before age 18 and CYP1A1-exon 7 polymorphism | • 5.65 (1.50-21.3)<br>• 3.61 (1.11-11.7) |
| Schernhammer et al., 2001 | • Work 1-14 years on rotating night shifts<br>• Work 15-29 years on rotating night shifts<br>• Work 30 or more years on rotating night shifts | • 1.08 (0.99-1.18)<br>• 1.08 (0.90-1.30)<br>• 1.36 (1.04-1.78) |
| Laden et al., 2002 | • Highest PCB serum levels and CYP1A1-exon 7 polymorphism in postmenopausal women | • 2.78 (0.99-7.82) |

III. Environmental Factors and Breast Cancer Risk in Maryland
U01 CA/ES62988
Principal Investigator: Kathy J. Helzlsouer, MD, MHS

| Study | Risk Factor(s) | OR (95% CI) |
|---|---|---|
| Wu et al., 1999 | • Lowest B12 serum levels in post-menopausal women from the 1974 cohort<br>• Lowest B12 serum levels in post-menopausal women from the 1989 cohort | • 4.0 (1.95-15.20)<br>• 2.25 (0.86-5.91) |
| Sato et al., 2002 | • Highest β-carotene serum levels in women from the 1974 cohort<br>• Highest lycopene serum levels in women from the 1974 cohort<br>• Highest total carotene serum levels in women from the 1974 cohort<br>• Highest lutein serum levels in women from the 1989 cohort | • 0.41 (0.22-0.79)<br>• 0.55 (0.29-1.06)<br>• 0.55 (0.29-1.03)<br>• 0.40 (0.17-0.98) |

IV. Organochlorine Compounds and Risk of Breast Cancer
U01 CA/ES62986
Principal Investigator: Tongzhang Zheng, MD, ScD

| | | |
|---|---|---|
| Zheng, Holford, Zahm et al., 2002 | • GSTT1 polymorphism in postmenopausal women<br>• Smoking before age 18 and GSTT1 polymorphism in postmenopausal women | • 1.9 (1.2-2.9)<br>• 2.9 (1.0-8.8) |
| Zheng, Holford, Mayne et al., 2002 | • Radiation treatment for skin problems in postmenopausal women<br>• Radiation treatment for skin problems six or more times in postmenopausal women<br>• Radiation treatment for skin problems six or more times and younger than 20 at first treatment in postmenopausal women | • 1.7 (0.8-3.6)<br>• 2.5 (1.0-6.8)<br>• 3.4 (0.9-12.7) |
| Zheng et al., 2001 | • Ever lactated in parous women<br>• Breastfeeding more than 3 children in parous women<br>• Breastfeeding first child for more than 13 months in parous women | • 0.83 (0.63-1.09)<br>• 0.53 (0.27-1.04)<br>• 0.47 (0.23-0.94) |
| Goodstine et al., 2003 | • Highest (n-3)/(n-6) polyunsaturated fatty acid (PUFA) ratio in premenopausal women<br>• Highest PUFA ratio when data were restricted to all women in the population-based study | • 0.59 (0.29-1.19)<br>• 0.50 (0.27-0.95) |

**Key terms:**

CYP1A1-exon 7 polymorphism = A to G transition allele
CYP1A1-MspI polymorphism = T to C transition allele
CYP17 polymorphism = A2 allele
NAT2 polymorphism = slow acetylators
CYP2E1 polymorphism = C allele
MnSOD polymorphism = A alleles
$ADH_3$ polymorphism = 1 allele
GSTT1 polymorphism = null genotype

**Appendix A References:**

Ambrosone CB, Freudenheim JL, Graham S, et al. Cytochrome P4501A1 and glutathione S-transferase (M1) genetic polymorphisms and postmenopausal breast cancer risk. *Cancer Res* 1995;55:3483-3485.

Ambrosone CB, Freudenheim JL, Graham S, et al. Cigarette smoking, N-acetyltransferase 2 genetic polymorphisms, and breast cancer risk. *JAMA* 1996;276:1494-1501.

Ambrosone CB, Freudenheim JL, Thompson PA, et al. Manganese superoxide dismutase (MnSOD) genetic polymorphisms, dietary antioxidants, and risk of breast cancer. *Cancer Res* 1999;59:602-606.

Freudenheim JL, Ambrosone CB, Moysich KB, et al. Alcohol dehydrogenase 3 genotype modification of the association of alcohol consumption with breast cancer risk. *Cancer Causes Control* 1999;10:369-377.

Goodstine SL, Zheng T, Holford TR, et al. Dietary (n-3)/(n-6) fatty acid ratio: Possible relationship to premenopausal but not postmenopausal breast cancer risk in U.S. women. *J Nutr* 2003;133(5):1409-14.

Hunter DJ, Hankinson SE, Hough H, et al. A prospective study of NAT2 acetylation genotype, cigarette smoking, and risk of breast cancer. *Carcinogenesis* 1997;18:2127-2132.

Ishibe N, Hankinson SE, Colditz GA, et al. Cigarette smoking, cytochrome P450 1Al polymorphisms, and breast cancer risk in the Nurses' Health Study. *Cancer Res* 1998;58:667-671.

Laden F, Ishibe N, Hankinson SE, et al. Polychlorinated biphenyls, cytochrome P450 1A1, and breast cancer risk in the Nurses' Health Study. *Cancer Epidemiol Biomarkers Prev* 2002;11:1560-5.

McCann SE, Moysich KB, Freudenheim JL, et al. The risk of breast cancer associated with dietary lignans differs by CYP17 genotype in women. *J Nutr* 2002;132(10):3036-41.

Moysich KB, Ambrosone CB, Vena JE, et al. Environmental organochlorine exposure and postmenopausal breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 1998;7:181-188.

Moysich KB, Shields PG, Freudenheim JL, et al. Polychlorinated biphenyls, cytochrome P4501A1 polymorphism, and postmenopausal breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 1999;8:41-44.

Sato R, Helzlsouer KJ, Alberg AJ, et al. Prospective study of carotenoids, tocopherols, and retinoid concentrations and the risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2002;11(5):451-7.

Schernhammer ES, Laden F, Speizer FE, et al. Rotating night shifts and risk of breast cancer in women participating in the Nurses' Heatlh Study. *J Natl Cancer Inst* 2001;93(20):1563-68.

Shields PG, Ambrosone CB, Graham S, et al. A cytochrome p4502E1 genetic polymorphism and tobacco smoking in breast cancer. *Mol Carcinog* 1996;17:144-150.

Wu K, Helzlsouer KJ, Comstock GW, et al. A prospective study on folate, B12, and pyridoxal 5'-phosphate (B6) and breast cancer. *Cancer Epidemiol Biomarkers Prev* 1999;8:209-217.

Zheng T, Holford TR, Zahm SH, et al. Cigarette smoking, glutathione-S-transferase M1 and T1 genetic polymorphisms and breast cancer risk. *Cancer Causes Control* 2002;13:637-45.

Zheng T, Holford TR, Mayne ST, et al. Radiation exposure from diagnostic and therapeutic treatments and risk of breast cancer. *Eur J Cancer Prev* 2002;11:229-35.

Zheng T, Holford TR, Mayne ST, et al. Lactation and breast cancer risk: A case-control study in Connecticut. *Br J Cancer* 2001;84(11):1472-6.

# Appendix B: Full List of Research Recommendations

**Cancer Registries**

- Link cancer registries to data from occupational, residential, and environmental records.
- Improve registries by mandating early reporting, including occupational data, and increasing privacy and access.
- Develop and apply geographic information systems (GIS), including the collection of historical community data.

**Breast Milk Research**

- Establish a national biomonitoring program to track exposures using analysis of breast milk and other biological specimens for biomarkers of community exposures.
- Create a computerized, Web-accessible, database for recording levels of environmental chemicals reported in human milk and infant formula in a standardized manner, with interpretation, in a manner inclusive of geographic locations.
- Determine the levels of environmental chemicals found in human milk and infant formula.

**Risk Factors and Exposures**

- Study suspected and known carcinogens, including pesticides, that have not yet been examined in relation to breast cancer risk (e.g. atrazine).
- Study the relationship between exposure to Epstein-Barr virus and breast cancer risk.
- Study occupational exposures, including light at night, and breast cancer risk.
- Study cigarette smoke, particularly passive exposure, and breast cancer risk.
- Study radiation use in medicine by health professionals and breast cancer risk.
- Study diet, particularly harmful contaminants in food, and breast cancer risk.
- Study traditional risk factors in light of environmental contaminants, including environmental hormones.
- Investigate synergistic effects between multiple exposures.
- Determine how the estrogen receptor status of tumors is related to risk factors for breast cancer.
- Study the relationship between breast developmental stages and breast cancer.
- Explore the impact of environmental factors on breast cancer survival.

**Research Methods and Design**

- Conduct large prospective cohort and/or collaborative studies designed to assess interactions between multiple environmental and lifestyle exposures and genetic characteristics.

- Study the relationship between breast cancer risk and exposures that occur at all ages and periods of life, such as adolescent exposures, childhood exposures, and *in utero* exposures.
- Study the interplay between the timing of events and chronic exposures.
- Design studies that compare areas of low and high breast cancer incidence.
- Study high-rate areas before and after cleanups of environmental contamination occur.
- Improve exposure assessment in population studies by developing methods for accurate determination of environmental exposures, spanning 20-30 years of an individual's life, relevant to breast cancer development.
- Develop better biomarkers for exposure, disease, and susceptibility.
- Design preventive studies and studies of potentially modifiable protective factors.
- Conduct occupational studies in women.

# Appendix C: National Centers of Excellence in Women's Health

Boston University Medical Center
Boston, Massachusetts

University of California, Los Angeles
Los Angeles, California

University of California, San Francisco
San Francisco, California

Harvard Medical School
Boston, Massachusetts

University of Illinois at Chicago
Chicago, Illinois

Indiana University School of Medicine
Indianapolis, Indiana

Magee-Womens Hospital
Pittsburgh, Pennsylvania

Virginia Commonwealth University
Richmond, Virginia

Brown University
Providence, Rhode Island

University of Arizona
Tucson, Arizona

MCP Hahnemann University
(Doing business as Drexel University)
Philadelphia, Pennsylvania

University of Michigan Health System
Ann Arbor, Michigan

University of Wisconsin, Madison
Madison, Wisconsin

University of Puerto Rico
San Juan, Puerto Rico

Tulane and Xavier Universities of Louisiana
New Orleans, Louisiana

University of Washington, Seattle
Seattle, Washington

University of Mississippi Medical Center
Jackson, Mississippi

University of Minnesota
Minneapolis, Minnesota

Oregon Health and Science University
Portland, Oregon

## Appendix D: Workshop Participants

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# Appendix E: Compiled Ranking Results of Recommendations on Risk Factors and Exposures

| | Rank 1 | Rank 2 | Rank 3 | Rank 4 | Rank 5 | Rank 6 | Rank 7 | Rank 8 | Rank 9 | Rank 10 | Rank 11 | Total Rank | Final Rank |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| carcinogens such as pesticides | IIIII IIII 9 | IIIII II 14 | IIII 12 | IIII 16 | II 10 | I 6 | I 7 | II 16 | 0 | 0 | 0 | 90 | 1 |
| viruses and autoimmune | I 1 | II 4 | I 3 | III 12 | II 10 | IIII 24 | IIIII II 49 | III 24 | II 18 | II 20 | III 33 | 198 | 9 |
| occupational exposures - light at night | I 1 | II 4 | IIII 12 | II 8 | IIII 20 | IIIII 30 | IIIII III 56 | III 24 | 0 | I 10 | 0 | 165 | 4 |
| smoking - passive and active | 0 | I 2 | 0 | II 8 | IIII 20 | IIIII I 36 | II 14 | IIIII 40 | II 18 | IIII 40 | IIII 44 | 222 | 10 |
| medical radiation | I 1 | IIII 8 | I 3 | II 8 | IIIII I 30 | II 12 | II 14 | IIIII 40 | III 27 | II 20 | II 22 | 185 | 8 |
| diet, obesity, and food contaminants | III 3 | III 6 | IIIII 15 | II 8 | IIII 20 | IIIII 30 | IIIII 35 | 0 | I 9 | II 20 | 0 | 146 | 3 |
| traditional risk factors | IIIII 5 | II 4 | II 6 | II 8 | IIII 20 | II 12 | IIII 28 | III 24 | III 27 | I 10 | II 22 | 166 | 5 |
| multiple exposures/ synergism | IIIII 5 | IIII 8 | IIIII 15 | IIII 16 | IIIII 25 | II 12 | I 7 | I 8 | 0 | II 20 | I 11 | 127 | 2 |
| estrogen receptor status | 0 | II 4 | 0 | II 8 | IIII 20 | II 12 | IIIII 35 | II 16 | IIII 36 | III 30 | IIIII I 66 | 227 | 11 |
| breast development | IIIII 5 | I 2 | II 6 | III 12 | IIIII 25 | II 12 | II 14 | I 8 | IIII 36 | IIII 40 | I 11 | 171 | 6 |
| environmental factors and survival | I 1 | II 4 | IIIII I 18 | IIII 16 | I 5 | II 12 | IIIII I 42 | III 24 | II 18 | I 10 | II 22 | 172 | 7 |

Tallies represent the number of participants who gave each recommendation a particular ranking. The numbers below the tallies were calculated by multiplying the number of tallies by the rank. Total rank was calculated by summing all of the numbers below the tallies for each recommendation. Final rank is the order of importance from 1 to 11. Final rank is based on the total rank; the lower the total rank, the lower the final rank.

**Final Ranking**

1. Study suspected and known carcinogens, including pesticides, that have not yet been examined in relation to breast cancer risk (e.g. atrazine).
2. Investigate synergistic effects between multiple exposures.
3. Study diet, particularly obesity and harmful contaminants in food, and breast cancer risk.
4. Study occupational exposures, including light at night, and breast cancer risk.
5. Study traditional risk factors in light of environmental contaminants, including environmental hormones.
6. Study the relationship between breast developmental stages and breast cancer.
7. Explore the impact of environmental factors on breast cancer survival.
8. Study radiation use in medicine by health professionals and breast cancer risk.
9. Study the relationship between exposure to viruses, autoimmune system, and inflammatory responses and breast cancer risk.
10. Study cigarette smoke, particularly passive exposure, and breast cancer risk.
11. Determine how the estrogen receptor status of tumors is related to risk factors for breast cancer.