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A Newsletter of the Cornell University Program on Breast Cancer and Environmental Risk Factors (BCERF)

Biomonitoring and Biomarkers Update

By Suzanne Snedeker, Ph.D., BCERF Associate Director for Translational Research

It has been five years since the Centers for Disease Control and Prevention (CDC) received funding to launch its Environmental Public Health Tracking Program, which includes the biomonitoring of blood and urine levels of environmental chemicals in the general US population. Recently the CDC released a report on the history of the tracking program and progress they have made toward making linkages between the environment and human health. Canada has recently announced the launching of a new biomonitoring program as part of a larger health survey being conducted from 2007-09. Researchers and medical professionals have projected new directions that can be taken in future to develop biomarkers of diseases, including cancer biomarkers and environmental biosensors. Summaries and commentary on all three of these areas are provided, plus an update by Sandra Steingraber on the new biomonitoring legislation in California.

Biomonitoring and Environmental Health Tracking in the US

The CDC has recently released a new report, *Keeping Track, Promoting Health* (hereafter *Keeping Track*), which highlights the history of the CDC's tracking program, as well as the successes and challenges of the first four years (2002-2006). This includes efforts devoted to designing, improving, and formulating the many components and infrastructure needed for the tracking program's operation and long-term sustainability. An executive summary of this report is available at http://www.cdc.gov/nceh/tracking/keepingtrack.htm, and the 53-page report is downloadable as a pdf file. Major elements of the report are outlined below.

The Gap. The concept of identifying chemical hazards and assessing impact on the health of both wildlife and humans was a relatively new idea when the Environmental Protection Agency (EPA) was created in 1970. However, creation of the EPA resulted in moving some of the responsibilities for monitoring public health as impacted by environmental factors from other federal public health agencies to the EPA. The CDC report, in summarizing the history of the tracking program, notes that by 1988 the Institute of Medicine of the National Academies issued a report stating that the public health system in the US had a poor infrastructure. One of its weaknesses was a "fragmented responsibility for environmental health" (page 12, as cited in *Keeping Track*). This was echoed in the Pew Environmental Health Commission's report issued in 2000. The Pew report documented an "environmental health gap" (page 13, as cited in *Keeping Track*). The US lacked basic information to link environmental hazards with chronic diseases. The Pew report's recommendation for an environmental public health tracking system ultimately lead to congressional funding for the CDC to establish such a program starting in 2002. The accomplishments of the CDC program fall into several categories.

Biomonitoring Program. The CDC wisely used an established survey, the National Health and Nutrition Examination Survey, to monitor the levels of environmental chemicals in a cross section of the general population every two years. The biomonitoring program has been expanded from monitoring 25 chemicals in the first biomonitoring report to 135 chemicals in the 2005 report. The 2007 report (not yet published) will provide data on monitoring 148 chemicals in blood and urine in the general US population. Age groups monitored range from young children to seniors, with additional data collection to determine levels of chemicals among certain racial/ethnic groups (Mexican-Americans, Non-Hispanic blacks, Non-Hispanic whites).

State and City Pilot Projects. *Keeping Track*

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states the premise that has driven early phases of the tracking program: local agencies understand local problems best, and can be the most efficient at monitoring and taking action on local environmental health concerns. But the CDC realized that states and cities needed resources to establish better ways to collect environmental data, and to make linkages with existing state databases that contain health and environmental endpoints. Hence the CDC funded a pilot study conducted in New York City that enabled investigators to link 15 different sources of information to track whether the misuse of pesticides could be linked to illness in children, as well as effects on fetal health. The CDC grant also supported programs to allow residents to report illegal use of certain pesticides, and to learn more about appropriate methods for pest control. According to the study's chief investigator Daniel Kaas, the study was an amazing success. "We were phenomenally successful in making a difference at the local level, increasing awareness, reducing hazards, and improving health" (page 2 of Prologue, *Keeping Track*). Other such pilot projects provided many states and several cities with resources to both improve their capacity to monitor environmental and health endpoints, and more importantly, provided funding to make connections between levels of chemicals in the environment and people, with actual health effects.

"Connecting the Dots" at the National Level. *Keeping Track* emphasizes that making connections is vital to understanding the total picture of how our environment may affect our health. Many times we don't make optimal use of existing data because of a failure to "connect the dots." Many federal agencies are already responsible for monitoring levels of chemicals in the environment: the EPA monitors air quality; the U.S. Geological Survey (USGS) monitors chemicals in waterways and wells, and the National Aeronautics and Space Administration (NASA) tracks geographic information on a spatial basis (called GIS). While much of this federal environmental data is public information, all of the different databases need to be looked at together to get a better picture of which chemicals are in the environment and what is the potential for exposure. And in order to interpret the data, levels in the environment and biomonitoring data in people need to be linked to existing health databases. The CDC discovered that linking environmental levels of chemicals to existing health data was, and remains, a real challenge. This is partly because health endpoint data (e.g. cancer diagnosis or mortality data, birth outcomes, poisoning data) is collected by cities, counties and/or states, or is a part of individual research projects. Confidentiality issues affect both access to data and to what extent health endpoint data is used. Different databases maintained by different states and municipalities may code information differently. *Keeping Track* relates the fundamental challenges of sharing data when one locale records information by street, and another by zip code. Current legal structures protect privacy, but can also restrict the accessing and sharing of information necessary to developing a national network of health-endpoint information. Despite these obstacles to connecting the dots, making strides toward bringing together existing data is crucial; CDC efforts to do so are described below.

Information Technology (the Sticky Web). One of the challenges being tackled by the CDC is how to best improve the ability to share health information across small networks (that will make up the larger network) while also protecting privacy. Developing methods to share, analyze, and interpret the data are hurdles that must be overcome in order to provide a usable system to track environmentally-related health outcomes. Such a networked system would work at the local and national levels to allow cities, states and federal agencies to quickly access information that can be used in real time, so community members and policy makers can be made aware of hazards, take preventative actions, and ultimately improve health. Many of the 2006 state grants have been awarded to improve information technology, laboratory capacity, and methods of communication so those who need the data can access it, interpret it, and take action. The report projects the ambitious plan that the Environmental Public Health Network will be ready to launch in 2008.

One More Step. We at BCERF strongly support the concept and share the common philosophy of providing sound information on the health risks of environmental factors so individuals, groups and policy makers can take action in their personal lives, workplaces, and communities to reduce the incidence of disease, including cancer. Yet one of the most difficult aspects of this work is tracking how people and organizations use cancer risk information we provide. The CDC faces a similar challenge in assessing the impact of the Environmental Public Health Network. Not only does the Network need to be carefully constructed, accessible, and well used, there needs to be a way to record what types of decisions are made as a result of accessing and using the information. Beyond communicating risk information, better methods are needed to capture how the information is used, and if the use of the network at the individual, city, state, and national level ultimately results in improved health over the short and long term.

Biomontoring in Canada

Health Canada has recently announced that they will conduct a national health survey in 2007-2009, *The Canadian Health Measures Survey*, which will include measuring environmental chemicals in blood and urine from a sample that represents the general Canadian population. It is anticipated that 5,000 male and female Canadians from ages 6 to 79 will participate in the survey, and a smaller subset will be monitored for levels of environmental chemicals. Questionnaires will also be used to provide information on environmental risk factors. The purpose of the biomonitor-

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Update on California's Environmental Contamination Biomonitoring Program

By Sandra Steingraber, Ph.D.

Suppose evidence emerges from studies of laboratory animals for a link between a particular chemical and early sexual maturation. Suppose this chemical is found in popular consumer products like, say, cosmetics. Or suppose it is a pesticide in widespread use. Could exposure to this chemical be playing a role in the falling age of puberty in US girls?

Without a biomonitoring program, there is no good way to answer that question. Evaluating the influence of chemical exposures on endpoints like pubertal timing is nearly impossible in the absence of a baseline for chemical exposure in infants and children. The US Centers for Disease Control (CDC) does monitor chemical contaminants in a representative sample of the US population, but the CDC's program collects very little data on infants and young children. And it does not target highly exposed populations for testing.

Enter the California Environmental Contamination Biomonitoring Program. In September 2006, California became the first state to mandate a statewide biomonitoring program. When fully implemented, it will test for the presence of environmental chemicals in the bodies of a representative sample of Californians throughout the state as well as initiate localized studies in communities of concern. Children of farm workers and nail salon workers could, for example, be identified as a subpopulation that could potentially benefit from biomonitoring.

Although late, the state's FY 08 budget did recently pass, containing a full $5.2 million for the program.

Governor Schwarzenegger had requested only $1.5 million for the first year. Most observers felt this was a paltry sum because it would only allow planning in Year One of the program. Subsequently, the Senate pro Tem Don Perata, who was the lead author on the bill creating the program, has been able to raise the proposed budget to $5 million. The $5.2 million which has been allocated should enable a good launch for the program, including the purchase of laboratory equipment.

The program is to be guided by a nine-member Scientific Guidance Panel, with four appointments from the Legislature and five from the Governor. The Senate Rules Committee has already named two appointments. They are Dr. Richard Jackson, former Director of the National Center for Environmental Health at CDC and currently Adjunct Professor at UC Berkeley's School of Public Health, and Dr. Gina Solomon, Assistant Clinical Professor of Medicine at U.C. San Francisco and Senior Scientist at the Natural Resources Defense Council.

Davis Baltz, the director of the Precautionary Principle Project at Commonweal in Bolinas, California and long-time watchdog of the biomonitoring legislative process, feels optimistic. "The program is an important milestone – it is the first statewide biomonitoring program in the country. It will generate important exposure information on environmental chemicals that we need but don't have, and it will likely spur legislative initiatives in other states."

Here are some key aspects of the program:

- The program does not restrict chemicals that can enter the program. There are permissive criteria that will allow the inclusion of chemicals of concern to the state. There is no requirement for a risk assessment to be performed before chemicals can enter the program.
- There is a right-to-know provision. The program will allow contributors (those providing their blood or urine) to receive results if they want them.
- The program's first priority will be to generate a statewide "snapshot" of environmental chemical exposure among Californians. In addition, the program will begin to plan for and then conduct smaller, localized community-based studies. Thus, California will be able to track statewide exposure trends over time, as well as investigate at highly exposed communities.
- The program represents a collaboration of three agencies. The lead is the California Department of Public Health, and the two others are both within the California Environmental Protection Agency: the Department of Toxic Substances Control (DTSC) and the Office of Environmental Health Hazard Assessment (OEHHA).

The new law's language can be found at:
http://www.leginfo.ca.gov/pub/05-06/bill/sen/sb_1351-1400/sb_1379_bill_20060929_chaptered.html

Sandra Steingraber, Ph.D., is a Distinguished Visiting Scholar at Ithaca College and former scholar in residence at BCERF. Her new monograph, ***The Falling Age of Puberty in U.S. Girls: What We Know, What We Need to Know****, is available free of charge from The Breast Cancer Fund* (www.breastcancerfund.org) *and is available for electronic download at* www.breastcancerfund.org/puberty/

ing component is to establish a baseline of the levels of chemicals in the bodies of Canadians, as well as providing data to allow comparison of levels with other countries, and in future to follow trends in the levels of the chemicals over time. Classes of chemicals that will be monitored include: metals, phthalates, polychlorinated biphenyls (PCBs), brominated flame retardants, organochlorine pesticides, organophosphate insecticide metabolites, phenoxy herbicides, continine, perfluorinated compounds, and bisphenol-A. The results of this study should greatly complement the existing CDC biomonitoring program, and will allow a greater ability to determine chemical levels in people living in North America. The study is described at: http://www.chemicalsubstanceschimiques.gc.ca/bio_e.html.

Cancer Biomarkers

Efforts to develop cancer biomarkers have been heralded as the new wave of research needed to facilitate cancer treatment as well as to predict how the environment may affect cancer risk. In an article written by William Dalton and Stephen Friend that appeared in the May 2006 issue of *Science*, the authors state that biomarkers provide a measurable reference for what is 'normal' and allow a frame of reference for predicting or detecting what is 'abnormal.' Genetic alterations in mutations, such as the BRCA mutations for breast cancer, specific proteins (prostate-specific antigens-PSA), as well as markers of circulating tumor cells have all been used in predicting cancer risk, while others like images (mammograms) are biomarkers used in detecting tumors. In their commentary, Dalton and Friend predict that new molecular technologies that will greatly expand the range of cancer biomarkers available may revolutionize cancer care in several ways: 1) detection of cancer at an early stage, especially in high risk individuals, 2) guide individual treatments based on the characteristics of that person's tumor, and 3) refinement of the genetic markers may facilitate the development of new drugs to treat cancer. Research to identify markers that can truly predict a patient's treatment response and identify those who will respond favorably to treatments has proven to be a challenge.

The original hope that scientists would find a single treatment response marker for a disease, they conclude, was at best naïve. It was found that early efforts to come up with biomarkers for the progression of diseases like breast and other cancers instead needed to looked at sets of genes, and carefully follow how up- and down-regulation of these genes changed as the disease progressed. Various research groups started to report on 'gene signatures' that predicted very aggressive types of tumors. But, wide variations in the sets of genes associated with these signatures were reported by different research groups. Hence, the scientific community is back at the drawing board trying to figure out why such variation occurred. The article mentions part of the variation may be due to different methods used to recruit subjects (enrolling all available versus specific age groups) and the methods different laboratories used collect and analyze the tumors.

According to Dalton and Friend, researchers have learned several lessons. One is the danger of oversimplification. Complex cancer biology can't be ignored; it has to be embraced. Biomarkers that can be applied to predict effectiveness of patient treatment will only be successful if markers are identified that include the wide molecular diversity of the disease and acknowledge that the biomarkers may change depending on the stage of the disease.

The other issue being faced is how to build full partnerships to share information while tackling issues of privacy and the pressures of intellectual property rights, both in academia and in industry. While this new frontier of molecular imaging holds great promise in detection, treatment, and ultimately understanding the basic biology of how cancer arises, a collaborative approach will be needed if the science is to be translated into practice.

Environmental Biomarkers (and beyond)

In a second commentary written by David Schwartz and Francis Collins (May 4, 2007 in *Science*), the authors envision a time when people may wear personal monitors with sensors that would collect information on exposure to chemicals, and provide information to your doctor on why you are sick and how you should be treated. Such sensors would integrate information on what you are exposed to, when you are exposed (in 'real time'), and your individual biological response. However, lessons can be learned from researchers in the cancer biomarker field. Complexity, biological diversity, wide variation in individual responses, and difficulties in sharing information will likely affect the field of environmental biomarkers in similar ways these components have affected advances in the cancer biomarker field.

While it is true that we are on the edge of a new type of science that may be able to determine and record how a chemical exposure affects a biological response and disease risk, is likely that we will not be able to interpret such data without conducting a number of similarly designed studies that document baseline responses, and the likely wide variation in responses between individuals exposed to the very same chemical. Schwartz and Collins acknowledge that there will be gene-related changes that occur after exposure to a chemical that the biosensor may record that have nothing to do with increased disease risk. There is likely to be considerable 'noise,' and research will be needed to characterize the sets of gene-related biological changes that predict disease risk. There will need to be considerable analysis of data to separate the wheat from the chaff, sharing of data across many disciplines, and monitoring of different at-risk populations over time in order to make sense of the data.

Those in the biosensing field can learn from those in the cancer biomarker field, that there will need to be standardization of methods, data collection, and data pooling, and new methods in computational biology to sift through

results. The immediate goal of developing panels of biomarkers for priority chemicals with known disease outcomes, and the future goal to develop sensors of emerging chemicals of concern should both be supported. I agree with the authors that if biosensing is to be validated to predict how environmental stressors affect or predict disease states, significant resources will have to be committed to this effort. However, a strategic plan to develop the framework needed to interpret the wealth of data that will come out of these studies also needs to be a priority.

Steps have been taken to support a multi-disciplinary approach. Schwartz and Collins describe a new effort they will co-chair, called the *Genes, Environment, and Health Initiative* (GEI). They discuss the training of scientists to think across disciplines and the creation of training opportunities in a new field, environmental genomics. The technology to achieve biosensing is fast approaching. The ability to translate the data into cancer prevention and public policy may be the larger challenge.

The Challenge: Understanding and Acting on Environmental Health Information

Our analytical and molecular genomic methods to collect biomonitoring and biomarker data have improved, but our ability to interpret data and relate it to predicting disease has lagged behind. While we have heavily invested in the technology to detect chemicals, biological responses, and genomic endpoints, similar resources on how to best interpret the data, how the data can and should be used for setting public health policy, and how to communicate results to the general public have not been allocated. The resources needed for interpretation, risk communication, dissemination, and documenting impact will be considerable. That is probably the lesson to be learned by all three approaches, from environmental health tracking, to cancer biomarker development, to environmental biosensors: we need better frameworks to interpret and communicate the data for using it to improve public health, and we need to commit the resources to do so.

In a recent analysis of the successes, challenges, and future efforts needed to sustain and extend the Environmental Public Health Tracking Program that appeared in the March 2007 issue of *the American Journal of Public Health*, study authors came to similar conclusions. They state that the "…ultimate measure of success in regard to the EPHT (*Environmental Public Health Tracking*) will be the translation of the data into effective prevention strategies. Ongoing evaluation of the ways in which surveillance and research results are being applied to prevent exposures, reduce adverse health risks, and improve environmental public health policies will be essential in providing the evidence base necessary to assess the impact and efficacy of EPHT."

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This article can be found on our website at:
http://envirocancer.cornell.edu/Newsletter/articles/v12Biomon.cfm

What's New on the Web

New Pages

Polybrominated Diphenyl Ethers (PBDEs)
Some PBDEs are estrogen mimics, and they have been widely detected in people and wildlife. We provide information on their risk, sources of exposure, and alternatives. Resources include the new *PBDE Brief*, links to newsletter articles, a PowerPoint slide show, and a comprehensive bibliography.
http://envirocancer.cornell.edu/pbde/

Updated Bibliographies

Inert Ingredients in Pesticide Products
http://envirocancer.cornell.edu/Bibliography/Pesticide/bib.inert.cfm

Women, the Workplace and Breast Cancer Risk
(Includes new section on airline attendants)
http://envirocancer.cornell.edu/Bibliography/Pesticide/bib.womenwork.cfm

http://envirocancer.cornell.edu

Other Web Sites of Interest

Silent Spring Institute
Mammary Carcinogens Database
Includes information on 215 chemicals known to induce mammary tumors in laboratory animals.
http://www.sciencereview.silentspring.org/mamm_about.cfm

Human Reviews Database
Includes 450 epidemiological articles on breast cancer, diet, lifestyle, body size, environmental chemicals, and physical activity.
http://www.sciencereview.silentspring.org/epid_about.cfm?new=1

The Recent Decline in Breast Cancer Incidence: What is its Relationship to Hormone Therapy Use?

By Barbour S. Warren, Ph.D., Research Associate, BCERF, and Carol M. Devine, Ph.D., R.D., Associate Professor, BCERF and Division of Nutritional Sciences

A report presented at the last San Antonio Breast Cancer Symposium in December 2006 (1) received a great deal of coverage in the popular press. Investigators utilizing the National Cancer Institute's SEER cancer registry reported a steep decline in the overall rate of breast cancer incidence between 2001 and 2003. Over this two-year period a decline of 7% was reported for women of all ages and tumor types. A decrease of this size was unprecedented. Of further surprise, an even greater decrease, 12%, was reported for the subgroup of women ages 50 to 69 with estrogen receptor positive tumors. The validity of this report has been confirmed by both earlier (2, 3) and subsequent reports (4-7) utilizing US cancer registries as well as those from other countries. These results reverse an 18-year trend from 1980 to 1998, over which breast cancer incidence increased by almost 40% (6). Although these changes have not been fully explained, this article reviews the potential explanations. Please see the box below for a description and definition of breast cancer incidence.

Breast cancer incidence decrease related to decrease in hormone therapy use: the evidence

Over almost the same time period that the breast cancer incidence decrease occurred, the number of annual prescriptions for hormone therapy after menopause (also known as hormone replacement therapy) dropped by 30% to 40% (9, 10). Most investigators agree that this large cessation of the use of hormone therapy plays the major role in the decreased breast cancer incidence. There is a substantial body of evidence supporting this conclusion.

First, long term use of hormone therapy containing estrogen and progestin has been well documented to cause breast cancer. In 2005, following review of existing evidence, the International Agency for Research on Cancer classified estrogen/progestin hormone therapy as "carcinogenic to humans" (11). This classification has been described as equivalent to a "case closed" determination for estrogen/progestin hormone therapy having a causative effect on breast cancer (12).

Second, as stated above, use of hormone therapy after menopause declined over a similar period as breast cancer incidence. This decline occurred following the failure of the first clinical trials examining hormone therapy for beneficial effects on coronary heart disease and osteoporosis. One trial was the Heart and Estrogen/progestin Replacement Study (HERS) which evaluated the effect of estrogen and progestin hormone therapy on women with existing heart disease (13, 14). No benefit was found, as benefits seen later in use were overridden by risk occurring during the first year of use. A second trial was the Women's Health Initiative (WHI) which examined both estrogen/progestin and estrogen alone hormone therapy for long-term prevention of coronary heart disease and osteoporosis (15, 16). Both the estrogen/progestin and estrogen alone arms of the WHI trial were terminated early when it became apparent that risks of the treatments exceeded their benefits.

The US national trends for the number of prescriptions written for hormone therapy (estrogen/progestin and estrogen alone therapy) increased by 54% from 1995 to 1999,

Breast cancer incidence

Most simply, breast cancer incidence is a measure of the level of occurrence of new cases of breast cancer during a given year. Formally defined, it is the number of cases of breast cancer that occur in a certain group of people during a specific year. Since incidence reflects an occurrence over a period of time, it can be considered a rate and is frequently called the incidence rate. To allow for comparison between different groups of people, incidence values are typically mathematically adjusted for size (per 100,000 people) and for differences in the numbers of people of different ages within the groups (age adjustment). The values used typically come from state and federally run registries that track the occurrence of different types of cancer. For example, the Centers for Disease Control, using data from the National Cancer Institute's SEER cancer registry, recently reported that for women age 50 to 59 living in the areas covered by this registry, there was 7.4% decrease in the incidence of invasive breast cancer between 2002 and 2003 (8). The invasive breast cancer incidence rate in 2002 for women age 50 to 59 (269.1 new cases of invasive breast cancer per 100,000 people) declined in 2003 to 249.1 new cases of invasive breast cancer per 100,000 people. Both these values were gadjusted to the age distribution, or fractions of the population in different age groups, seen in 2000 for the US population.

but from 1999 (one year following the HERS report) to 2002 they remained stable (9). However, between 2001 and 2003, following the WHI termination, they plummeted to 63% of their starting value. The decline in use of estrogen/progestin therapy was even greater, ending in 2003 at a number 28% of the 2001 annual rate.

As the above discussion indicates, there was little to no lag between the decreases in hormone prescription and the decline in breast cancer incidence. Such a change was not without precedence. A similar change in incidence was seen in the late 1970s following a large decrease in prescription of estrogen-only hormone therapy after it was associated with a very strong increase in the risk of uterine cancer (17). As will be discussed below, the rapid decline in breast cancer incidence is also biologically credible.

Third, the key role played by hormone therapy in the recent decrease in breast cancer incidence is also supported by a substantial body of observational evidence showing an association between hormone therapy and increased breast cancer risk. Almost 20 case control and cohort studies have examined the association of hormone therapy and breast cancer risk. In the vast majority of the studies estrogen/progestin therapy was found to moderately increase breast cancer risk (18). The majority of the studies also reported similar findings for estrogen-alone hormone therapy which, because of its very strong association with uterine cancer, was only prescribed to women without a uterus (18). As discussed above, the WHI trial provided a causative link between estrogen/progestin therapy and breast cancer risk. However, unlike the epidemiological studies, the WHI trial did not find a causative link between estrogen-alone therapy and breast cancer risk. This difference is currently unresolved.

Fourth, the level of decrease in breast cancer incidence has been demonstrated to vary in populations with different levels of hormone therapy use. A well-conceived study in California examined the incidence of breast cancer and survey-reported use of estrogen/progestin hormone therapy between 2001 and 2004 for 58 counties in California (19). They found that: 1) those counties with the least reduction in use of hormone therapy had an 9% decrease in breast cancer incidence; 2) those counties with an intermediate decrease in hormone therapy had a 14% decrease in breast cancer incidence; and 3) those counties with the largest decrease in hormone therapy had a 23% decrease in breast cancer incidence. This study indicates not only a link between hormone therapy and breast cancer incidence but, more significantly, a quantified link.

Fifth, the biological plausibility for a connection between the recent decline of hormone therapy use and breast cancer incidence is also good. Estrogen and progestin function as tumor promoters for breast cancer formation (20). A key characteristic of carcinogenic promoters is the requirement of repeated exposure. Some scientists describe this as promoters "fueling" tumor growth. In the absence of these "fuels," tumors stop growing and can potentially regress. Studies of cancer incidence found that tumors which expressed estrogen receptors were affected to a much larger degree by the use of hormone therapy. Such an outcome would be expected in an environment where breast tumor growth was "fueled" by estrogen- and progestin-containing hormone therapy. These results provide additional support for a role of decreased use of hormone therapy in this decline in breast cancer incidence.

Epidemiological studies have also provided supporting evidence from cohort and case control studies which evaluated changes in breast cancer risk after hormone therapy is stopped. These studies have found that the risk of breast cancer is greatest during hormone therapy use and following termination of use risk decreases to control levels over a five-year period (21, 22).

Other possible contributors to decline in breast cancer incidence

While reduction in the use of hormone therapy is likely to have played the major role in the decline in breast cancer incidence, other contributors have also been mentioned. These include inaccuracy in the cancer registry data, a decrease in the number of women getting mammograms, changes in the use of tamoxifen or roloxifen, and changes in risk factors associated with breast cancer risk.

Inaccuracy of cancer registry data is highly unlikely to have contributed to the breast cancer incidence decrease. Beyond the fact that cancer registries in the US are considered very accurate, the effect of hormone therapy on breast cancer incidence has been reported in data from a number of different cancer registries in both the US and other countries (2-7). It is not likely that similar inaccuracies would be found in multiple registries.

Changes in the number of women getting mammograms may have contributed to the decline in breast cancer incidence, as cancer incidence rises and falls with the number of women examined. However, the contribution of changes in mammography to this phenomenon is likely to have been very small. The rate of mammography in the US during 2002 to 2003, when the decreases in breast cancer incidence occurred, fell only of a few percentage points (23). Small decreases such as these would be expected to have little effect on breast cancer incidence.

The use of tamoxifen and roloxifen did not change over this time period (4). Thus, population-wide changes in the use of these estrogen antagonists cannot be linked to the drop in breast cancer incidence.

Clearly, these alternative factors could at best act as minor contributors for the recent decline in breast cancer incidence. Accordingly, the decreases in the use of hormone therapy in response to the negative results from the HERS and WHI clinical trials are almost certainly responsible for the decline in breast cancer incidence. The story does not end here; there are a number of important questions that remain.

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Remaining questions regarding breast cancer risk and mortality, and hormone therapy

First, how is breast cancer incidence expected to change from this point forward? This is unclear. Some have proposed a continued decrease in breast cancer incidence to a new and lower level. Others have predicted that established tumors will grow at a slower rate in the absence of hormone therapy and that incidence levels will rise again albeit less dramatically. These changes will, no doubt, be closely monitored in the future.

Second, it will be important to evaluate how and if these changes will affect overall death rate from breast cancer. This effect is also unclear. Since decreases were seen in the both the tumors which respond well and poorly to therapy, there is potential for future decreases in the breast cancer death rate. A change in breast cancer prognosis is also possible as the decrease in cancer incidence was greatest for estrogen receptor positive tumors. These tumors have much better treatment outcomes and their decrease may lead to change in the overall percentage of tumors responding well to therapy.

Finally, it is important to examine the size of the impact of hormone therapy on public health. This is best done using an epidemiological calculation known as the population attributable fraction or PAR. The PAR is best understood as the fraction or percentage of breast cancer cases that would be theoretically eliminated if a certain risk factor (hormone therapy) was eliminated. The PAF, in this case, would be calculated from the prevalence of hormone therapy use and the risk of breast cancer linked to this use. A PAF between 8% and 15% has been determined for estrogen /progestin hormone therapy (12, 20, 24). These values agree well with the changes in incidence reported to date. These values also indicate that over the 7.5-year period that a combined estrogen /progestin pill (1995) was approved to the WHI cessation (mid-year 2002) more than a 100,000 breast cancer cases could be related to estrogen/progestin hormone therapy (12).

When the WHI was being planned, so strong was the belief in the benefit of hormone therapy that some investigators protested that the trial would be unethical as the control group would be receiving a placebo drug (25). In hindsight, we can be ever so thankful that that this idea was overridden.

This article can be found on our website at:
http://envirocancer.cornell.edu/Newsletter/articles/v12Decline.cfm

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Nutrition's Role in Safeguarding Against Environmental Toxicity and Associated Diseases

By Jennifer L. Wilkins, Ph.D., R.D., Senior Extension Associate, Division of Nutritional Sciences, Cornell University

Hennig, B., Ettinger, A. S., Jandacek, R. J., Koo, S., McClain, C., Seifried, H., Silverstone, A., Watkins, B., and Suk, W. A. (2007) Using Nutrition for Intervention and Prevention against Environmental Chemical Toxicity and Associated Diseases, *Environmental Health Perspectives*, 115, 493-495.

When many people choose to eat a nutritious diet – one with plenty of fruits, vegetables, and whole grains, and limited added sugars, saturated and trans fats – feeling good and living a long and healthy life are key motivators. But in this paper, *Using Nutrition for Intervention and Prevention against Environmental Chemical Toxicity and Associated Diseases*, the researchers offer yet another good reason for getting your "five-a-day": the potential for wise food choices to protect against diseases that are associated with exposure to toxic chemicals and other environmental pollutants.

We know from research that exposure to environmental chemicals and pollutants is a contributing factor in poor health and the development of many diseases. In today's world it's difficult to avoid toxic chemicals and other pollutants. In the United States poorly managed hazardous waste sites and the use and accumulation of chemical pollutants represent a growing challenge to environmental quality and to public health. Many pollutants, such as heavy metals and persistent organics, concentrate in our bodies. So far eliminating pollutants from the environment, or preventing them from getting there in the first place, has proven either too difficult or too costly to avoid completely. Thus, making lifestyle choices to minimize their health impacts makes sense. What diet one follows is one of these important choices.

Despite decades of research that has lead to a sophisticated understanding of the connection between nutrition and health, diet-related chronic diseases remain the single largest cause of death and illness among Americans. Diet is among several factors – including environmental exposures and genetic disposition – that contribute to the development and progression of age-related chronic diseases.

The research paper reviewed here provides compelling argument for further exploration into the interactions between environmental exposure, nutrition, and disease risk and the need for better tools to evaluate these interactions. Diet appears to play at least two important roles in the outcome, and indeed incidence of these interactions.

First, depending on the specific foods eaten, one's diet can actually be a source of exposure to environmental toxic pollutants. Because many pollutants are fat soluble, foods high in fat – such as some meats, dairy products and certain species of fish – can contain higher levels of persistent organics than "plant foods" – vegetables, fruits, and grains.

The second way diet plays a role is in its influence on an individual's nutritional status which determines one's lipid profile, oxidative stress, and antioxidant levels within cells. Such alterations at the cellular level can negatively impact biological processes, and in turn, magnify the potential for environmental pollutants to cause disease or dysfunction.

The authors cite several studies suggesting how diet and nutrition ameliorate (or exacerbate, in some cases) the impact toxic pollutants can have on human health.

Some studies reveal that toxic effects of dioxin and similar compounds stem from their activation of the aryl hydrocarbon receptor (AhR). Interestingly, some dietary components also activate AhR but do not lead to a toxic effect. Why? Research suggests that when dioxin and its cousins turn AhR on, it stays active leading to toxic effects. Components in the diet, however, have a short-lived affect on AhR. This temporary activation, research suggests, might avoid toxic effects while promoting health benefits.

Other studies provide evidence that various nutrients and phytochemicals – healthful chemical compounds found in plant foods – are strong antioxidants with anti-inflammatory effects. Since inflammation is known to be an underlying factor in diet-related diseases – including cardiovascular

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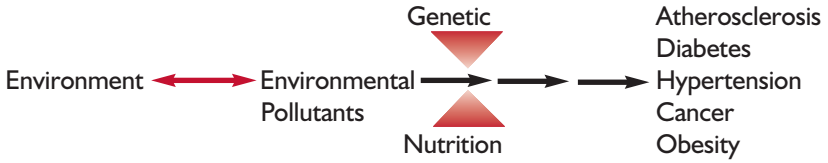
This simple model from the commentary illustrates the relationship of the toxicology of environmental pollutants to disease and how health impacts of these exposures can be modulated by genetics and nutrition.



More than 40,000 Women Have Joined the Sister Study

10,000 Sisters still needed to help find the causes of breast cancer.

The National Institute of Environmental Health Sciences (NIEHS) needs 10,000 more women to join the Sister Study, the nation's largest research effort to find the causes of breast cancer.

Barbara Moore, left, and her sister Mary Catherine.

Barbara Moore (see photo) is one of almost 2,000 participants from New York. "My sister Mary Catherine wasn't aware that she had breast cancer until it was late stage. She had a mastectomy in 2003, and on Thanksgiving of that year she passed away. I was devastated. We were so close. The Sister Study said they were looking for the *causes* of breast cancer. That really caught my attention."

Now helping with recruitment herself, Ms. Moore will be addressing BCERF's Regional Cancer and Environment Forum on September 27 in New York City, hopefully reaching potential Study participants, or those who can relay the message to possible recruits.

Since its national launch in October 2004, The Sister Study has recruited more than 40,000 participants – women whose sisters were diagnosed with breast cancer. Recruitment is far from over. NIEHS hopes to enroll a total of 50,000 women whose sisters had breast cancer. The Sister Study must meet its enrollment goal by the end of 2007.

"Many women have heard about the Sister Study, but they haven't signed up yet, and we really need them now," said Dale Sandler, Ph.D., Chief of the Epidemiology Branch at NIEHS and Principal Investigator of the Sister Study. "Doctors know very little about how the environment may affect breast cancer, that is why the Sister Study is so important. We hope women will make that call today," she added.

The Sister Study requires very little time from its volunteers, and volunteers can participate in either English or Spanish. The 10-year observational study begins with participants answering questions about diet, jobs, hobbies, and things they've been exposed to throughout their lives to determine what may influence breast cancer risk. Later, at a convenient time and location for the participant, a female health technician collects small samples of blood, urine, toenail clippings, and house dust, which will also help give researchers a better picture of the woman's environment and genes.

Women in the U.S. and Puerto Rico, ages 35 to 74, may be eligible to join the Sister Study if their sisters (living or deceased) had breast cancer. Women who join the Sister Study must never have been diagnosed with breast cancer themselves. Breast cancer affects women from every walk of life, so the Study is seeking women of all backgrounds, occupations, ages, and ethnic groups. The Sister Study is tailoring its recruitment efforts to help ensure the needed mix of women.

Women in trades and industry. Ms. Moore learned about the Sister Study at the Coalition of Labor Women (CLUW) convention in Detroit in 2005, where women working in trades and industry could be reached. These women – including those in non-traditional trades – have powerful information to share with the Study. Sara Williams leads the effort to recruit Native American Sisters and Women in Trades. Says Ms. Williams, "Women working in trades may encounter hazardous exposures at work. They may lead stressful lives trying to balance work and home life. Or, they may be more physically active or fit than other women because of their job requirements. All of these factors may be important in determining who will or will not develop breast cancer. The Sister Study is designed to better understand which factors increase the chances of developing breast cancer and which factors may reduce the chance of developing this disease."

Native American women. "Sadly, women are not equal when it comes to breast cancer risk," explains Ms. Williams. "The five-year survival rate for Native American women is lower than that of other ethnic groups in the United States. Although the breast cancer mortality rates for most Native Americans is lower than those for white, African American, and Hispanic women, the rate of death due to the disease has risen since the 1970s in selected areas of the United States." Currently over 550 Native American women are enrolled.

Senior women. Senior women are particularly encouraged to join. Older women have a longer history of living and working in a variety of surroundings, than the younger women in the study. Breast cancer risk increases steeply with age, and the risk of developing breast cancer is greatest for women over the age of 65. Also, factors that have been linked to breast cancer risk differ for pre-menopausal and postmenopausal women. It is important for older women to participate in studies like the Sister Study so that we can better understand why they are at increased risk.

African American women. Says Dr. Sandler, "African American women often face breast cancer at a younger age, have more aggressive tumors, and have the highest breast cancer death rate of women in the US." "If you're a woman of color whose sister had breast cancer, your participation in the Sister Study is especially important," continued Dr. Sandler. "We want to learn more about how to protect your daughters and your granddaughters from this devastating disease."

Other important recruitment efforts target Latina sisters, and Asian and Pacific Islander sisters. Ada Pacheco is another participant from New York, who was born in Puerto Rico. She says with regard to her sister who developed breast cancer, "We grew up together, went to the same school, shared the same bedroom, clothes, friends…everything! I joined the Sister Study because I hope this research will help find what causes breast cancer so we can help prevent it in future generations. I need to know why my sister had breast cancer and not me. We were born in the same place, raised together, ate the same food…why Carmencita and not me?"

The Sister Study follows sound, ethical research practices, and keeps all personal data safe, private and confidential. Women who join are ***not*** asked to take any medicine, visit a medical center, or make any changes to their habits, diet or daily life.

Says Sara Williams, "If every woman in the study looks like me – a middle-aged white woman with a desk job – we won't gain new information to benefit *all* women in the United States. Most of what we now know about breast cancer comes from studies of white women. The sad reality is that breast cancer knows no social, economic, or racial boundaries. It is my greatest hope that women from all walks of life will take part in this landmark study and help unravel the mystery of a disease that kills over 40,000 women in our country every year."

This article can be found on our website at:
http://envirocancer.cornell.edu/Newsletter/articles/v12Sister.cfm

Organizations that are in partnership with the Sister Study include the American Cancer Society, NIH's National Center on Minority Health and Health Disparities, Sisters Network Inc., Susan G. Komen for the Cure, the Y-ME National Breast Cancer Organization, and the Intercultural Cancer Council. In addition to working with its national partners, the Sister Study works with local, regional, and national organizations to inform diverse women about the study.

To volunteer or learn more about the Sister Study, visit the web site www.sisterstudy.org, or for Spanish visit www.estudiodehermanas.org. A toll free number is also available 1-877-4SISTER (877-474-7837). Deaf/Hard of Hearing call 1-866-TTY-4SIS (866-889-4747).

Nutrition's Role in Safeguarding Against Environmental Toxicity and Associated Diseases
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disease, diabetes, arthritis, osteoporosis, and cancer – diets rich in phytochemicals (such as flavonoids) can provide protection against environmental toxicants that diminish antioxident levels in the body.

Herbal remedies and nutraceuticals may also play an important role in the nutrition, diet, environmental toxin effects relationship. For example, polyphenols, especially catechins found in green tea, can inhibit intestinal absorption of lipids and lipid-soluble compounds (such as persistent organic pollutants) and enhance their elimination from the body.

Even very familiar nutrients, such as calcium, have been shown to be important in this regard. Calcium has been found to be an effective treatment for moderately high cumulative lifetime exposure to environmental lead pollution. Research conducted on pregnant and lactating woman in Mexico showed an association between calcium supplementation and decreased maternal blood lead levels. It would be interesting to learn if calcium obtained through food – both dairy and non-dairy sources – confers the same effect.

The authors present a strong case for further research into the many ways that diet and nutrition can either reduce exposure to environmental toxins or help reduce the likelihood they will induce age-related chronic diseases. This is an important area of research since human consumptive behavior results in a wide range of pollutants. Globally, as more countries gain economic power, the environment will sustain an even greater burden and overall exposure will increase. Learning how to better arm ourselves against the resulting pollutants through changes in diet seems a wise and necessary approach. The health effects associated with exposure to polychlorinated biphenyls, for one example, may increase as a result of ingestion of certain dietary fats, but eating more fruits and vegetables, rich in antioxidant and anti-inflammatory nutrients or bioactive compounds, may prove to be protective.

Adoption of such practices for the sake of self-preservation will ultimately fail, however, without efforts pursued in tandem – and with greater intergovernmental cooperation – to protect and restore the health and vitality of the ecosystem. After all, the foods that make up the diets we hope will enhance our health and reduce chronic disease risk depend on continuing availability of viable, sustainable, and non-toxic natural resources. Further elucidation of dietary approaches that can ameliorate the effects of pollutants should not make us complacent about their sources and the need to reduce them. In order to keep producing crops that are healthful,

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Nutrition's Role in Safeguarding Against Environmental Toxicity and Associated Diseases *continued from page 11*

raising animals that are healthy, and catching fish that are safe and abundant, environmental stewardship and conservation need to remain a top priority.

Dr. Jennifer Wilkins is a Senior Extension Associate in the Division of Nutritional Sciences at Cornell, where her work focuses on the linkages between human, environmental, and community health through sustainable food systems. Dr. Wilkins developed the first regional food guide in the United States, the Northeast Regional Food Guide, which promotes health, sustainability, and local food systems. She directs the Cornell Farm to School Program and the Farmers Market Nutrition Program. Dr. Wilkins writes a column called "The Food Citizen" which appears in the Albany Times Union the first Sunday of every month.

This article can be found on our website at:
http://envirocancer.cornell.edu/Newsletter/articles/vl2RCNutrition.cfm

The Recent Decline in Breast Cancer Incidence: What is its Relationship to Hormone Therapy Use? *continued from page 8*

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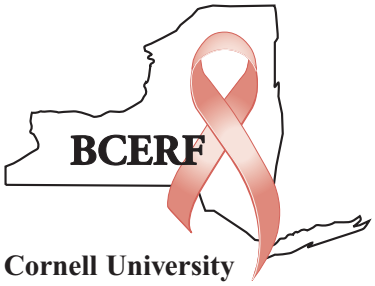

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