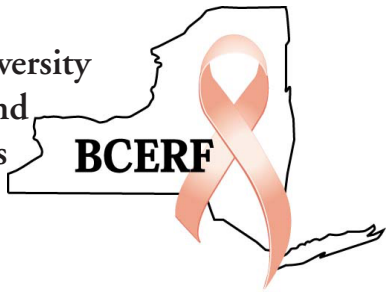
The Ribbon

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



Volume 7, Number 4, Early Winter 2002

Evaluation of the Evidence: What Does it Take to Show a Cause-Effect Relationship Between Carcinogen Exposure and Cancer Formation?

Barbour S. Warren, BCERF Research Associate and
Carol M. Devine, BCERF Education Leader and Associate Professor, Division of Nutritional Sciences

Following the recent publication of findings from the Long Island Breast Cancer Study Project (see related article plus http://www.cancer.gov/cancerinfo/LIBCSP), a number of newspapers and magazines published articles and commentaries about the importance and impact of this study. Whether they approved or disapproved of the study, these articles generally overestimated the impact of a single study. Most of the articles about the study gave the impression that the results of a single study can determine if there is a cause-effect relationship between exposure to a specific chemical and changes in breast cancer risk. Some of these articles even went so far as to suggest that this single study provided conclusive evidence about the cause-effect relationship between all environmental contaminants and breast cancer. Missing from most of this coverage was the placement of this article in the context of how epidemiological cause-effect relationships are established and the contribution of a single study to understanding of this relationship. We hope to clarify these issues by describing the scientific evidence that is needed before a cause-effect relationship can be established.

This recently reported part of the Long Island Breast Cancer Study Project was conducted to determine whether there was an association between women's blood levels of various organochlorine toxins and their risk of getting breast cancer. An association (which was not found) would have shown that there was a connection or linkage between the event (exposure) and the disease (breast cancer) and that this association would not be expected to have occurred by chance. But the finding of an association, however strong, does not necessarily mean that the exposure causes the disease. An example of this involves the epidemiology of the birth of children with Down's syndrome. In this case, there is a strong association between the risk of a child having Down's syndrome and the child having a late birth order (being born late into the family and having a number of older siblings). Yet the cause of Down's syndrome is the addition of an extra copy of chromosome number 21. The association of Down's syndrome with birth order is observed because this extra chromosome occurs more frequently in older women, and the mothers of children late in the birth order are usually older. Being a later child does not cause the syndrome, it is only associated with it through the connection with older mothers.

Determination of a cause-effect relationship for a disease, or as it is frequently called in epidemiological

circles, causality, is arrived at by the evaluation of the results from a large number of studies of the epidemiology, as well as basic biology of the disease. A set of standards for assessing causality were first formally set forth by a panel organized by the US Surgeon General during the 1960s. These standards established a set of experimental results which should be met to conclude that there is a cause-effect relationship between an event (exposure) and formation of a disease. Evaluation of how well these standards are met allow for determination of the strength of the evidence for exposure and disease associations. The standards are now known as the criteria for causality. The criteria relevant to our discussion are listed in the table below.

The Criteria For Causality		
Evidence for a Cause-Effect Relationship Exists Between an Exposure and a Disease		
1	Consistency of the Association	The results of most studies agree using different methods and examining different groups of people.
2	Strength of the Association	The associated risk is strong enough to meaningfully affect the occurrence of the disease in real-life settings.
3	Dose Relationship for the Association	There is a clear trend in the size of the risk of the disease that increases (or decreases) with the extent of exposure.
4	Plausibility of the Association	The biological effects of the exposure can be sensibly related to formation of the disease.
5	Time of Exposure for the Association	The time between the exposure and occurrence of the disease agrees with the time required for development of the disease.

The following sections will discuss the key elements of these criteria. This discussion will use as an example the association between alcohol consumption and breast cancer risk. Alcohol consumption was chosen as an example because it is generally accepted to be associated (albeit moderately) with breast cancer risk.

1. Consistency of the Association

If there is a cause-effect relationship it is expected that the results of most studies will be consistent. But a frustration frequently encountered by both scientists and non-scientists alike is the inconsistency of the results of studies examining the association of various exposures to the risk of various types of cancer. It is not unusual to find conflicting results. Some studies may report no association or a negative association between an environmental exposure and cancer risk while other studies may report a positive association with cancer risk. A number of factors produce these inconsistencies. The major contributing factors include the relatively low risk associated with many environmental exposures, the difficulty of assessing exposure due to the long period of time required for cancer development, and differences in experimental design (discussed below in more detail).

This lack of consistency provides a good example of the necessity for good scientific judgement in the evaluation of evidence. In many cases inconsistency arises from weakness in the study design. The best studies: a) look at a large number of women who are representative of the larger population; b) accurately measure their exposure and when it may have occurred; c) account for the contribution of established risk factors to the breast cancer observed; and d) use a comparison (control) group of women who ideally differ only in the presence of the disease. In addition, studies that collect information from healthy women and subsequently follow them over time for the occurrence of the disease are considered to have less chance for bias. In some cases, elimination of weaker studies that do not meet these good design characteristics will resolve the inconsistency of association across studies. However, the size of the change in risk commonly seen with environmental exposures is also a contributor to this inconsistency. Thus, consistency would only be expected between studies examining a large number of women.

For example, there is consistency in the results of the many studies examining alcohol consumption and breast cancer risk. Out of 35 studies (of various designs and conducted in various countries), 26 found an increase in risk for women who drank the most. Nonetheless,

seven studies reported no effect of alcohol consumption on breast cancer risk and two studies reported a decrease in risk. This amount of inconsistency is not surprising considering the size of the risk associated with this exposure. There is about a 40% increase in the relative risk of breast cancer for women who have about four drinks daily. Nonetheless, the association of alcohol consumption with breast cancer risk is considered to be one of the most consistent of the dietary factors contributing to breast cancer risk.

2. Strength of the Association

The criteria for causality also predict that there will be a strong association between exposure and disease when there is a cause-effect relationship. The term "strong" must be seen as a relative one in this context and the values for environmental exposures are viewed accordingly.

Individual environmental exposures have not been associated with large increases in breast cancer risk. But it is important to realize that epidemiological studies use the term "environmental exposures" as a broad catch phrase which includes exposures from air, water, and food, as well as lifestyle (such as smoking and drinking). This is not to imply that these environmental exposures do not have a substantial contribution to the incidence of breast cancer. The most accurate studies examining the contribution of environmental factors to breast cancer risk were conducted examining the differences in cancer diagnosis between identical and non-identical twins. This recent large study of twins in Sweden, Denmark, and Finland (547 pairs of identical twins and 1075 pairs of non-identical twins) reported that about three-quarters of all risk for breast cancer was due to environmental exposures. The low level of risk seen for individual environmental exposures is possibly due to differences in susceptibility between women and to the individual environmental exposures acting through interactions between themselves and with other factors rather than alone.

Typically in evaluating the strength of environmental associations, changes in risk less than 20% are viewed as suspect. Statistical significance of the results is needed to assure that they are not due to chance alone. The risk of lung cancer for heavy smokers provides a good reference value. The relative risk of lung cancer-for heavy smokers (40 cigarettes/day) is 1000% to 2000% higher than the risk for non-smokers. Environmental exposures that are associated with an increase in breast cancer risk are much smaller. Using our alcohol consumption example, a study which pooled the data from six large, well-designed studies (including 322,647 women, 4335 with breast cancer) reported a 40% increase in breast cancer risk among women who had between two and five drinks a day. Alcohol consumption also provides a good example of the interactive nature of exposures. Several recent studies have reported significantly increased breast cancer risk among women who consume alcohol and also have a diet low in the B vitamin folic acid.

3. Dose Relationship for the Association

In most cases, the effect of a toxic agent increases with the dose or level of exposure; the causal criteria state that evidence for a dose relationship should exist. Most epidemiological studies divide the women studied into groups depending on their level of exposure. The level of risk is frequently calculated by comparing the risk of women with no or least exposure with those who had the highest exposure. However, examinations also evaluate trends of increased or decreased risk accompanying changes in exposure. The presence of such a trend or dose relationship provides good evidence for the validity of the finding.

There is a well-established dose relationship between alcohol consumption and breast cancer risk. Several studies have found that breast cancer risk increases with the amount of alcohol a woman consumes each day. In the pooled data study described above, breast cancer risk increased 9% for each 10 grams of alcohol (about one drink) a woman consumed each day. Accordingly, women who consumed four drinks per day would be expected to have 40% higher breast cancer risk than women who did not drink.

4. Plausibility of the Association

This criterion states that if there is a cause-effect relationship between a toxic exposure and risk of disease there should be supporting evidence from study of the effects of the toxic substance in cells, animals and humans. In other words, the effects should make biological sense.

For the association of alcohol consumption and breast cancer risk there is a large amount of supporting biological evidence that the association makes biological sense. Alcohol affects breast cancer risk factors (mammographic density and estrogen levels), mammary tumor formation in animals, dietary factors which are thought to be cancer preventive, and various changes at

the cellular level. Each of these effects support the linkage to cancer formation.

5. Time of Exposure for the Association

This criterion is built around the idea that disease processes have a latency period, a period of time between beginning of the disease process by the toxic exposure and the appearance of disease itself. An exposure which has a cause-effect relationship with a disease should occur at a time which agrees with the time period needed for formation of the disease. A latency period is especially important for breast cancer where the time period for disease formation is measured in decades. For example, a recent exposure is unlikely to be associated with the formation of cancer and would be viewed with skepticism.

The evidence for meeting this criterion for alcohol consumption and breast cancer risk is less strong than that for the other criteria. A number of studies have addressed this issue by examining if there are certain ages where alcohol consumption leads to the largest increases in breast cancer risk. Almost equal numbers of studies have found no period of highest risk as have found drinking at ages less than 25 or 30 to be linked to higher risk. Interpretation of this evidence is complex since there are studies to suggest that alcohol may act at more than one stage of the cancer formation process. It could act at an early or an intermediate time point.

The criteria for causality define the experimental results needed to conclude that there is a cause-effect relationship, but knowledgeable judgment is also required for this evaluation. This is because the body of scientific evidence on almost any issue is usually incomplete as well as flawed.

Scientific studies do not proceed in a highly systematic manner with these standards being examined one by one. Rather, the forces that guide what studies are conducted are based on a number of factors including the availability of funding, the number of investigators with expertise to conduct the studies, the access to subjects for study and the likelihood of a significant finding. These forces produce a body of evidence which may be very strong for some of the criteria and weak or non-existent for others. Accordingly, evaluations must be made by examining the strength of the total body of evidence and the degree to which it meets the standards that would result if a cause-effect relationship existed.

In conclusion, determination of cause-effect relationships requires a substantial body of evidence as well as knowledgeable evaluation of this evidence. Individual studies comprise small pieces of the large body of evidence needed and the answers to these complex questions are arrived at only after a great deal of study and many trials and errors. It is our hope that this article will give you the tools to see the forest (evidence needed for cause-effect relationships) rather than the many trees (results of individual studies of risk associations) for the various risk associations that are reported in the popular press.

The complete *Environment and Breast Cancer: Teaching Tools for Change* is now available at a reduced rate. Contact Jennifer Holton at JLH97@cornell.edu or (607) 254-2893 for more information and watch the BCERF web site for an interactive "Tool Kit Tour" in early 2003.

Environmental Chemicals and Breast Cancer Risk: Where Have We Been and Where Are We Headed?

Suzanne M. Snedeker, BCERF Director of Translational Research

When I started my career as a senior staff fellow at the National Institute of Environmental Health Sciences (NIEHS) in the late 1980s, I often started my talks with the following quote from cancer researchers Irma and Jose Russo:

> "The complexity of breast cancer and our failure to stop the 120,000 cases (1987 figures) that strike American women annually, or the fact that one out of four women will die as a consequence of it, is basically rooted in our lack of knowledge of the disease."

Fifteen years later, the Russo quote is still apt. We still do not have a complete picture of the biology of this disease nor of the many factors that affect breast cancer risk. The American Cancer Society predicts that in the year 2002 over 205,000 new cases of breast cancer will be diagnosed in Americans and 40,000 will die of the disease.

It is unfortunate that the media has given the impression that few environmental factors have been associated with human cancer. The World Health Organization's International Agency for Research on Cancer (IARC) has identified 80 natural and synthetic chemicals, occupational situations, pharmaceuticals and viruses that cause cancer in humans. For most cancers, we do not have exposure data or cancer risk data in humans. The National Toxicology Program has successfully used screening tests in rodents to identify potential human carcinogens. Of the 509 compounds evaluated, nearly 9% (42) have been identified as causing mammary (breast) tumors in laboratory rodents. The types of chemicals include industrial chemicals, dyes, flame retardants, solvents, pesticides, toxins from molds, and pharmaceuticals (See BCERF Fact Sheet #45, *Environmental Chemicals and Breast Cancer Risk; Why is There Concern?*, http://www.cfe.cornell.edu/bcerf/FactSheet/General/fs45.chemical.cfm)

It is not possible for one study to provide all the data needed to fully identify causes of breast cancer or explain the rising incidence rates. We cannot paint the picture of breast cancer in a single stroke. Rather, each study contributes a small piece to the mosaic of breast cancer risk. Each piece starts as a question, a hypothesis, based on the best information available at that time.

During the early 1990s, the results of several studies suggested that a high blood level of DDE, the metabolite of the persistent pesticide DDT, was associated with a higher risk of breast cancer. DDT and other persistent organochlorines, such as chlordane and dieldrin, were known to cause other types of cancers. Therefore, it was logical to pick these chemicals as factors to study in relation to breast cancer risk. These chemicals are also stored in body fat and can be easily measured in blood or fat samples.

The hypothesis of whether blood or fat levels of organochlorine pesticides or industrial contaminants (such as polychlorinated biphenyls, PCBs) predict breast cancer risk was tested in over 30 other studies, and most recently in the Long Island Breast Cancer Study Project (LIBCSP). Most studies of white Western adult women have not shown that blood levels of these compounds predict breast cancer risk. It is still unclear whether women of other ethnic backgrounds may have a higher breast cancer risk from past or current DDT exposure, or whether exposure during early periods of breast development affects later risk. (see BCERF Fact Sheet #2, *DDT, DDE and the Risk of Breast Cancer*, http://www.cfe.cornell.edu/bcerf/FactSheet/Pesticide/fs2.DDT.cfm). For other chemicals, including polyaromatic hydrocarbons, the LIBCSP results suggested a modest increased breast cancer risk (about 50% higher) associated with exposure to these compounds which are found in burned fossil fuels, cigarette smoke, and charred foods.

Dr. Mary Wolff, one of the co-authors of the organochlorine and PAH paper for the LIBCSP recently discussed the results and the analyses still underway for the LIBCSP at a Health Science Advisory Board meeting

(HSRB). While the media has given the impression that all results have been published, this is not the case. Important analyses on interactions between genes that activate cancer causing chemicals and breast cancer risk are still being compiled. The LIBCSP needs to be embraced as an evaluation of important hypotheses. Results of this study will ultimately add to our mosaic of knowledge about breast cancer. Because several chemicals were not associated with breast cancer, we should not abandon all research on how environmental factors affect the risk of breast cancer. On the contrary, it should force us to refocus our thinking, our approach, and refine the tools and methods needed to test future hypotheses.

For example, the timing of exposure to environmental factors affects future breast cancer risk. Japanese infants and girls exposed to ionizing radiation at Nagasaki and Hiroshima subsequently had a very high breast cancer risk compared to women who were over 40 when exposed. Recent research suggests high exposure to the environmental contaminant dioxin in younger women may increase breast cancer risk later in life. Silent Spring Institute researchers are characterizing household exposures to environmental toxins in women with and without breast cancer on Cape Cod. The Agricultural Health Study is evaluating whether exposure to agricultural chemicals affects health, including cancer risk, in over 85,000 men and women in farm families from North Carolina and Iowa. The Sister Study will follow over 50,000 sisters of women with breast cancer in an attempt to identify causes, including possible environmental links, to the disease. The results from these studies will better inform regulatory agencies and at-risk populations of the environmental factors that do and do not pose a cancer risk in target populations.

Much media attention has focused on the role cancer activists and policy makers play in influencing funding for cancer research. In 1899, a doctor from western New York wrote a essay published in the *Transactions of the Medical Society of New York* on possible causes of the rapidly rising rates of cancer. Because of this concern, he mentioned how a modest laboratory had been established dedicated to investigating the causes and treatment of cancer. He wrote, "…as the result of persistent efforts on the part of a number of men, both professional and laymen, both in and out of the Legislature, the Legislature of New York appropriated a small sum for the purpose of equipping and maintaining a laboratory devoted to this kind of (cancer) research." This modest cancer laboratory located in Buffalo, New York has grown into the prestigious cancer research center named after the author of the essay, Dr. Roswell Park.

Over the last year I was invited to attend a series of workshops held at the National Institute of Environmental Health Sciences. Scientists, risk assessors and cancer activists engaged each other in a full discussion of approaches that could be used to better evaluate and understand the role of environmental factors in breast cancer risk. This November, I attended an international symposium in Oxford, England that brought international scientists from many different disciplines together to discuss the role of pesticides in cancer risk. Such interaction and partnerships at the local and global level are instrumental in enabling us to foster research agendas that will ultimately lead to risk reduction strategies for ourselves and our children.

Professor Ron Gorewit Working in Affiliation with BCERF Translational Research Faculty

Ron Gorewit has been on the Cornell faculty since 1975. He is currently a Professor in the Department of Animal Science. Prior to coming on board at Cornell, he established a diversified background in Biological Sciences. After receiving his B.S. in Biology at the University of California, Irvine he found his way to Michigan State University (MSU) in East Lansing, Michigan where he obtained his M.S. in Microbiology and Public Health. Dr. Gorewit's M.S. research project was in the area of cellular immunity, in which he worked on a project dealing with the human blood-born tropical parasite called *Leishmania donavani.* About the time he was about to receive his first graduate degree, his interests turned toward physiology (the study of organ systems). He was fortunate to receive a fellowship to study for his Ph.D. under the direction of H. Allen Tucker, a well-known and respected mammary gland biologist. Dr. Gorewit completed his Ph.D. on the

physiological and biochemical role of adrenal gland hormones on mammary gland development, as well as the initiation and maintenance of lactation.

His research focus at Cornell has dealt with several aspects of mammary gland biology, ranging from hormonal control of mammary gland growth, development and function to the influence of stress on milk secretion and removal. Dr. Gorewit has been an author on over 100 scientific papers and is both nationally and internationally respected in the field of mammary gland biology. He is currently focusing his research efforts in the areas of biologically active/ medicinal/anti-cancer components found in milk, and the influence of environmental chemicals on mammary gland growth, development, function and disease. In addition, he will be working in affiliation with BCERF developing critical evaluations on the cancer risk of two persistent, endocrine disrupting pesticides, hexachlorobenzene and beta-hexachlorocyclohexane. These cancer risk evaluations will be 'translated' into fact sheets for use by consumers and health educators.

"We Need to Know"

Ad Hoc Discussion Group

"Learning Together"

The Ad Hoc Discussion Group meeting took place on October 18, 2002 at the new office of the Breast Cancer Coalition of Rochester (BCCR). Holly Anderson, BCCR Executive Director warmly welcomed the group, as did Aide to Congresswoman Louise Slaughter, Patty Larke. Ms. Larke provided a very thoughtful opening to the meeting, with remarks on the status of research on breast cancer and environmental risk factors, with special reference to that area of research which the meeting would focus upon, early exposures.

Activities in the Rochester area. Several presentations from local participants provided a picture of related community activities in the Rochester area. Holly Anderson of BCCR described the scope of activities of this dynamic group. Many BCCR members were in attendance, and some had an opportunity to describe additional projects they were involved in; for example, with regard to carcinogens in the community.

Drs. Dina Markowitz and Katrina Smith Korfmacher of the Community Outreach and Education Programs of the University of Rochester Environmental Health Sciences Center described their activities and publications. For example, they shared their newsletter, *Choices: Bringing Environmental Health into the Classroom*, one of several initiatives which helps teachers and students address complex environmental health issues.

Participants learned a lot about efforts to address health and safety problems for the farmworker population in the region. James Schmidt of Farmworker Legal Services of New York, Inc., and Michel Attia, of Rural Opportunities, Inc. described their respective work, emphasizing those projects which address reducing pesticide exposures among this at-risk population.

Research focus: early life exposures and breast cancer risk. The afternoon was organized around the theme of early life exposures and breast cancer risk. BCERF's Barbour Warren set the stage for the subsequent presentations by providing an introduction and overview of this area of research. Dr. Warren explained the biology of "windows of vulnerability;" that is, why certain periods of life present unique susceptibility with regard to problematic exposures.

Dr. Tom Gasiewicz, the Deputy Director of the University of Rochester Environmental Health Sciences Center, contributed to the day with his presentation on "The Effect of Dioxin Exposures on Developing Tissues, with Emphasis on the Immune System and Cancer Response." Dr. Gasiewicz presented many "knowns" with regard to dioxin exposure effects, as well as emerging data and research gaps. He described effects that his research was revealing that are specific to the exact day of prenatal development on which an exposure occurs.

BCERF's director Rod Dietert then spoke on federal government research activities with regard to fetal and childhood exposures. For example, he described the National Children's Study, which will examine the

effects of environmental influences on the health and development of 100,000 US children, to be followed until age 21. He also described activities taking place on the federal level relating to revisions of guidelines for setting "reference doses," emphasizing the complexity of this process with regard to latency concerns; that is, how little we know about early exposures that may cause changes not obvious until much later in life.

Input regarding future Ad Hoc Discussion Group meetings? Please contact Carmi Orenstein at (607) 254-2893 or cso1@cornell.edu

New Fact Sheet

- Fact Sheet #46 on *Smoking and Breast Cancer Risk*

Please find this new fact sheet on our web site at: http://www.cfe.cornell.edu/bcerf/ or call the BCERF office if you have no web access and need a printout. (BCERF will no longer be printing fact sheets. Limited supplies of some previous fact sheets will continue to be available.)

The Ribbon is published by the Cornell Program on Breast Cancer and Environmental Risk Factors in New York State. Comments are welcome; contact the Editor.

Editor
Carmi Orenstein, M.P.H., Assistant Director
Associate Editor and Designer
Carin Rundle, Administrative/Outreach Coordinator

Cornell University
Program on Breast Cancer and Environmental Risk Factors in New York State
112 Rice Hall, Cornell University
Ithaca, NY 14853-5601

Phone: (607) 254-2893
FAX: (607) 255-8207
E-Mail: breastcancer@cornell.edu.

CORNELL Cooperative Extension