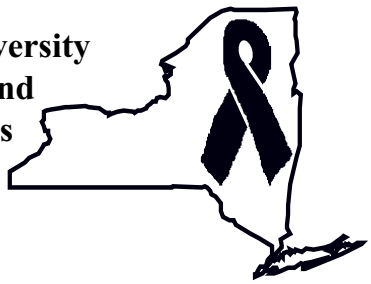
The Ribbon

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



Volume 3, Number 3, Summer 1998

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Contributions of Experimental Animal Research to the Understanding of Human Breast Cancer

What causes breast cancer? Is there something that can prevent it, or cure it? Researchers are using many different approaches and sophisticated techniques to answer these questions. The current fast-paced and highly technical world of scientific research makes it very difficult to keep up with all of the new information. Some knowledge about the scientific process, experimental design, and data interpretation may provide non-scientists with an appreciation for and greater understanding of breast cancer research.

There are many different ways to study breast cancer. One way is to examine the association between the disease and various biological and environmental factors through epidemiologic studies. The key features and specific examples of epidemiologic studies were recently reviewed in Volume 3, Number 1 of *The Ribbon*. Other types of studies rely on animal models and/or isolated breast cells or other kinds of cells grown in the laboratory (cell culture studies). Laboratory studies that use animal models of breast cancer are the focus of this article. Look for an article on cell culture and similar studies in a future issue of *The Ribbon.*

All basic scientific studies follow a similar plan. They start with a hypothesis, based on previous observations and the results of other animal, cell culture or human studies. A hypothesis is an assumption that a scientist makes. The next step is to design an experiment to test the hypothesis. There is no general set of guidelines to follow for designing a good scientific experiment, and what is considered "good" depends on the type of experiment being done. In this article, the important features of two different kinds of animal experiments are discussed, as well as how they contribute to the understanding of human breast cancer.

Animal studies are an important part of breast cancer research because they offer scientists a way to ask questions about cause, prevention and treatment in a controlled environment. In epidemiologic studies, scientists have to account for natural differences in their sample of the human population. For example, there are individual genetic differences among people that may account for how an individual reacts or responds to a carcinogen or to a cancer treatment. Also, the scientists may not know what people were exposed to during periods of their lives outside of the experimental time frame. Finally, it is not possible or ethical to control all aspects of a person's diet and/or lifestyle choices or to expose her/him to a suspected carcinogen. In animal studies, scientists have more control over all of these situations and this is a major advantage.

Although there are some obvious biochemical and physiologic differences between animals and humans, there are more similarities. Therefore, although results from animal tests are never directly extrapolated to humans, animal and human cancer studies are closely related to and dependent on each other. Advances in the knowledge of breast cancer are made by combining the results from animal and human, as well as cell culture, studies.

Scientists use animal models of breast cancer in many different ways including to: 1) test the carcinogenicity of a chemical; 2) determine if a chemical acts like the hormone estrogen; 3) determine if a particular food or a natural chemical in that food may prevent the development of breast cancer; 4) test if a new drug is an effective treatment for breast cancer; and 5) learn more about the basic molecular and biochemical mechanisms underlying the cancer process. An animal study designed to test the effectiveness of a new anti-cancer drug is discussed in the "Research Commentary" section of this issue. In this article, two other types of animal studies, the long-term cancer bioassay and nutrition studies, are discussed. For the cancer bioassay, we highlight some of the critical features required to make this type of experiment valid. For the nutrition study, we use an example to illustrate one approach to this type of experiment.

The Cancer Bioassay

Scientists use the cancer bioassay to determine if a particular chemical is a potential carcinogen. Because of the importance of this type of study to human health, many different organizations such as the World Health Organization (WHO), the Environmental Protection Agency (EPA), the International Agency for Research and Cancer (IARC), and the National Toxicology Program (NTP) have contributed to the development of guidelines for the design and interpretation of experiments to test the carcinogenicity of a chemical. A study designed to test the carcinogenicity of a chemical must follow these guidelines in order to be considered an appropriate cancer bioassay.

In the U.S., the majority of cancer bioassays to test for a pesticide's cancer causing potential are either conducted by the NTP, or through industry contracts established to meet the EPA's requirements for health effects assessment for pesticide registration. Most of these studies are not published in the scientific literature. However, abstracts of the NTP studies are available on the web: http://ntp-server.niehs.nih.gov/main_pages/NTP_ALL_STDY_PG.html. Organizations such as IARC and the EPA analyze the results of all relevant studies before evaluating a chemical's carcinogenicity. BCERF offers a unique assessment of chemical carcinogenicity with specific reference to breast cancer through critical evaluations of the research on pesticides and other chemicals. Some of the requirements of the cancer bioassay that BCERF considers when evaluating a study are described below.

Cancer bioassays must be conducted in accredited laboratories to ensure that proper animal care, housing, and feeding are taking place. A cancer bioassay should be conducted in more than one animal species — typically mice and rats. In each of these species, both male and female animals should be included. Finally, the cancer bioassays require a larger number of animals compared to other animal experiments. Usually at least 50 animals per dose are needed to do the proper statistical analysis for tumor incidence.

There are other important considerations regarding the design of the cancer bioassay. First, the scientists must correctly administer the chemical to the animals using the route most likely experienced by a human population. Two acceptable routes of administration include ingestion and inhalation. Sometimes it is acceptable to apply the carcinogen to the skin. Injection of the animal with a carcinogen is not an appropriate route of administration and may cause other side effects.

Different doses of the potential carcinogen are used to see if there is a dose-response effect and to generate a dose-response curve for cancer risk assessment. One group of animals does not receive any of the carcinogen and they serve as the controls. It is particularly important that the control animals are obtained from the same facility as the experimental animals and that they are the same strain and age. In addition to the control group, there are at least three treatment doses. The highest dose needs to be the "maximum tolerated dose" (MTD). This dose is defined as the dose required to cause a 10% to 15% decrease in body weight gain without significantly affecting the survival of the animals.

The animals in the cancer bioassay need to be exposed to the potential carcinogen for at least 24 months to allow enough time for tumors to develop. After tumor formation, it is important for the scientists to evaluate

Definitions

In vivo: in the living body. An experiment in an animal model is referred to as an *in vivo* experiment.

In vitro: in an artificial environment. An experiment in a test tube or cell culture system is an *in vitro* experiment.

Dose: refers to the concentration or amount of a drug, chemical or food given to an animal (*in vivo*) or added to cells in culture (*in vitro*).

Inbred strain of rats: a population of laboratory rats derived from a small set of ancestors. These animals are more closely related genetically than if mating had occurred by random selection.

The Organization of a Scientific Paper

After completing a study, a scientist usually communicates the results to the rest of the scientific community by writing a research paper. These papers are reviewed by other scientists before publication. Most of these papers are organized as follows:

Introduction: In this section, the scientist provides background information to place his/her work in the proper context. Also, the hypothesis being tested is usually stated here.

Methods: This section contains a description of the experimental design. It usually contains details of all the materials and procedures used.

Results: The scientist will describe the results of the experiment using words, graphs and pictures when necessary.

Discussion: In this section, the scientist will attempt to explain the results of the experiment. This may involve discussing any limitations of the study as well as putting the results into the context of other previous studies described in the introduction. Then some conclusions can be proposed and suggestions made for future studies.

References: The scientist will list the previous studies that he/she referred to throughout the paper.

them using pathologic criteria; for example, to determine the incidence and type of benign and malignant tumors.

The cancer bioassay is an important method to identify potential human carcinogens. Regulatory agencies use the information obtained from animal cancer bioassays in combination with results from other experiments, such as epidemiologic studies, to evaluate the cancer causing potential of a chemical or pesticide.

Nutrition Studies

Information from several different types of epidemiologic studies has indicated that diet may be very important for both the prevention and treatment of breast cancer. This observation has led to hypotheses and experiments using animal models of breast cancer to specifically test various components of the human diet.

♦ ***EXAMPLE***: **Brussels sprouts**

The investigators in this study (Stoewsand et al., 1988) hypothesized that brussels sprouts are protective against mammary carcinogenesis (breast cancer). In contrast to the cancer bioassay, there are no established guidelines to follow for the experimental design of an animal nutrition study. Although these types of studies are important in the field of breast cancer and other chronic diseases, they are not contributing information to help determine whether or not a chemical is a health threat to human beings. Therefore, scientists who conduct these studies are not held to the same set of rules and are more free to creatively investigate methods of prevention.

To test their hypothesis, the scientists used 60 female Sprague-Dawley rats. This is because mammary tumors in rats mimic breast cancer in humans and the tumors are similarly affected by genetic, hormonal, dietary and environmental factors. Scientists use inbred strains of rats, such as Sprague-Dawley, because they are very genetically similar.

In this type of study, there is no specific number of animals required as in the cancer bioassay. Instead, scientists choose a number of rats based on their calculation of the number necessary to generate sufficient statistical power. This is also important in epidemiologic studies. As in the carcinogenic bioassay, all of the rats were the same age, and had the same access to food and water. The scientists chose to induce the formation of mammary tumors by using a drug called 7,12-dimethylbenz[a]anthracene (DMBA), a synthetic chemical used in experimental studies that is known to cause mammary tumors. By using this method, the scientists did not have to wait for tumors to develop spontaneously or naturally, and they knew when the mammary tumors were initiated.

The rats were divided into 4 groups of 15 rats each as follows: 1) Group A was fed a diet that consisted of 20% dried brussels sprouts, and they received a dose of DMBA; 2) Group B was fed a diet that consisted of 20% brussels sprouts, and they did not receive any DMBA; 3) Group C was fed a regular rodent diet, and they received a dose of DMBA; and 4) Group D was fed a regular rodent diet, and did not receive any DMBA. Several weeks into the experiment the diets were switched, and Groups A and B were fed a regular diet while Groups C and D were fed a diet that consisted of 20% brussels sprouts. This experiment was designed to determine if and when during the cancer process — at initiation, promotion, or progression — brussels sprouts would be most effective. The rats were weighed during the experimental time frame because it is important to determine if the dietary intervention also affected their growth and weight. The scientists checked for tumor formation by touch, but then confirmed their reports by looking at the tumor cells under a microscope and defining them by pathological criteria.

The researchers found that the rats who were fed brussels sprouts early in the experiment were less likely to develop cancerous tumors as compared to the rats fed brussels sprouts only late in the experiment. There was some evidence that the mammary tumors shrank in the rats fed

brussels sprouts later in the experiment. This suggests that brussels sprouts are very effective early in the cancer process when the tumors are being initiated. They are somewhat less effective in preventing tumor progression or promoting tumor regression. The investigators also reported that there was an increase in the number of benign tumors in the rats fed brussels sprouts early in the experiment as compared to later in the experiment.

This study provides some good and positive information on the cancer preventing potential of brussels sprouts, but also leaves some questions unanswered. To put the results in the proper context, there are some limitations of the study that need to be considered. For example, rats don't normally eat brussels sprouts and the diet of the animals fed the brussels sprouts may be different in several ways from the diet of the animals fed the regular rodent chow. When the scientists added the brussels sprouts, they had to remove some other dietary components. Also, the scientists only looked at one concentration or dose of brussels sprouts, 20%. Future experiments might try to determine if a different dose of brussels sprouts would still be effective against the development of cancerous tumors, but not promote the formation of benign tumors.

The evidence from this study, future animal studies, and epidemiologic studies should be considered together before reaching any conclusions regarding the amount of brussels sprouts in a human diet needed to help prevent the development of breast cancer.

The results of both cancer bioassays and nutrition studies need to be considered within the framework of the strengths and limitations of the experimental method. Then this information should be combined with the results from human and cellular and molecular studies to design better prevention, treatment and diagnosis strategies for breast cancer.

Written by Julie Napieralski, BCERF Research Associate

Reference

Stoewsand, G. S., J. L. Anderson, and L. Munson (1988) Protective effect of dietary brussels sprouts against mammary carcinogenesis in Sprague-Dawley rats. Cancer Letters, 39: 199-207.

Research Commentary

Anti-Angiogenic Drugs

The news: A front-page article in the *New York Times* on May 3, 1998 reported that angiostatin and endostatin, two substances produced by a tumor itself, can cause tumors in mice to shrink when given at artificially high concentrations.

Is this research new? No! There were no new findings that were reported to the media on May 3rd. Two papers in leading scientific journals *Cell* and *Nature* had reported on the anti-tumor effect of angiostatin and endostatin in mice in 1997 (O'Reilly et al., 1997; Boehm et al., 1997). The motivation behind the recent media focus was not clear, since no new research announcements had been made to the press.

What is angiogenesis? A small tumor is a cluster of abnormally replicating cells, and can survive using the normal blood supply of its host organ. However, for a tumor to grow and progress further, it needs blood to reach the rapidly dividing cells deep within it. To meet this need, the tumor stimulates the growth of new blood vessels—a process called angiogenesis. Simultaneously, many tumors produce inhibitors of angiogenesis, such as angiostatin and endostatin, to inhibit the growth of blood vessels. Researchers believe that by producing a balance of stimulators and inhibitors, tumors regulate the growth of new blood vessels, and prevent the overgrowth of blood vessels.

The research behind the news: Two scientific papers published in 1997 described how anti-angiogenic drugs act. In the first paper, O'Reilly et al. (1997) used recombinant DNA technology to put the mouse endostatin gene into bacteria, and produce larger quantities of endostatin in bacteria. This mouse endostatin was harvested and injected into mice. All the mice tested had been treated with tumor causing agents and had tumors of a specific size already. Ten milligrams of endostatin, for every kilogram of body weight of mouse, was found to inhibit tumor growth and even reduce the size of existing tumors. The treatment was effective against many different tumors tested in mice — of skin, lung, blood and fibrous tissue. No side effects were noticeable in the endostatin treated mice. The tumors did not grow for as long as the endostatin injections were continued.

Besides being very effective, anti-angiogenic drugs were found to have an additional advantage over conventional chemotherapy. Many tumors can initially be controlled with the chemotherapeutic drugs to which they respond. However, tumor cells change and adapt very fast. Most

failures of cancer treatment occur when the tumor cells acquire resistance for the chemotherapeutic drugs that were keeping them in check. Anti-angiogenic treatments target stable normal cells and not the fickle tumor cells. Hence, the frequency of acquiring tolerance to this treatment is expected to be low. In the second paper, Boehm et al. (1997) demonstrated that even after many repeated treatments with endostatin, tumors continued to shrink and did not acquire resistance or tolerance for this particular therapy.

Recent unpublished reports at scientific meetings indicate that a combination of angiostatin and endostatin is more effective against tumor growth. A new study published in *Nature* (July 17, 1998), reports that the combined use of radiation and angiostatin is more effective in mice than either therapy alone. There are also many reports of other anti-angiogenic drugs being evaluated against tumors.

Related research: Related research indicates that recombinant human angiostatin (rather than the mouse version) is also effective in inhibiting tumors in mice (Lannutti et al., 1997; Sim et al., 1997). It is also encouraging to note that the endostatin protein produced by mice is very similar in composition to that produced in humans (Saarela et al., 1998; Standker et al., 1997). However, all the trials so far have been in one experimental model (mice) and it is too early to predict if the anti-tumor effects would also occur in humans. It would be useful to know if the human angiostatin works similarly against tumors in other mammals such as rats or rabbits. The big question, to which no one yet has any answer, is if the human body can tolerate such artificially high levels of these inhibitors.

What is the forecast for this therapy? The first step, on which scientists are already working, is the large-scale production of the human and mouse versions of these drugs. When this step is successful, the drugs will have to be critically analyzed for toxic impurities. Only then can a human clinical trial begin. The National Cancer Institute predicts that even if all goes smoothly, it will be at least a year before clinical trials are possible. We are at least three to five years away from the time when these drugs would be available for cancer patients.

Written by Renu Gandhi, BCERF Research Associate

References

Boehm, T. et al. (1997). Antiangiogenic therapy of experimental cancer does not induce acquired drug resistance. Nature *390*, 404-407.

Lannutti, B.J. et al. (1997). Human angiostatin inhibits murine hemangioendothelioma tumor growth in vivo. Cancer Research *57*, 5277-5280.

Mauceri, H.J. et al. (1998). Combined effects of angiostatin and ionizing radiation in antitumour therapy. Nature *394*, 287-291.

O'Reilly, M.S. et al. (1997). Endostatin: An endogenous inhibitor of angiogenesis and tumor growth. Cell *88*, 277-285.

Saarela, J. et al. (1998). Complete primary structure of two variant forms of human type XVIII collagen and tissue-specific differences in the expression of the corresponding transcripts. Matrix Biology *16*, 319-328.

Sim, B.K.L. et al. (1997). A recombinant human angiostatin protein inhibits experimental primary and metastatic cancer. Cancer Research *57*, 1329-1334.

Standker, L. et al. (1997). Isolation and characterization of the circulating form of human endostatin. FEBS Letters *420*, 129-133.

"We Need to Know"

Ad Hoc Discussion Group

"Learning Together"

On July 9, 1998, the BCERF Ad Hoc Discussion Group meeting was held in White Plains, NY, attended by fifty people. BCERF thanks the New York Hospital-Cornell Medical Center for the use of their facilities, and Congresswoman Nita M. Lowey (D, NYS 18th Congressional District) for welcoming participants and introducing this meeting of the Ad Hoc group.

Congresswoman Nita M. Lowey. Congresswoman Lowey spoke from the perspective of a policymaker and a woman in Congress. She highlighted accomplishments in the area of breast cancer research over the past several years, and challenges still ahead. The Congresswoman remarked that BCERF's work "is unique in its focus on making information about risk factors available to public health professionals and the general public." She has been able to secure federal funding for BCERF for the past three years, and told the group that she remains committed to continued investment in this work.

Congresswoman Lowey discussed federal government changes in both attitude and actual allocation of dollars, with regard to breast cancer research. Involvement of breast cancer advocates in decisions about how to allocate federal research monies is also an important development at the national policy level. "Advocates," she said, "are

From Left to Right: Congresswoman Nita M. Lowey, June Fessenden MacDonald, BCERF Director, Stephen P. Johnson, Cornell Office of Government Affairs Director

adding a fresh perspective to review panels, helping scientists and administrators look at their research portfolios in important new ways." Despite these many accomplishments, Congresswoman Lowey warned that "this is not the time to slow down our efforts."

Director's Report. BCERF Director June Fessenden MacDonald opened by reviewing BCERF's goals and then highlighted progress since the last meeting of the group. Some research highlights include: Critical Evaluations on the pesticides lindane and 2,4-D have been posted on the BCERF web page for a 30-day public comment period, and the Environmental Risk Factors Database now contains over 1,900 entries. June also described progress on the revamping of the BCERF web site (see What's New on the Web), and the publication of twelve new fact sheets (see tear sheet). Also on the education front, new BCERF health educator Mary Maley and BCERF Education Project Leader Carol Devine are working on a rural initiative, to bring tailored information on breast cancer risk reduction to women in rural areas of New York State. BCERF public education efforts are encouraged by the results of a recently completed telephone survey which indicated that participants in 1997 training programs are applying the knowledge they gained from these programs in a variety of professional settings.

Farm Women Study. Betsy Lewis-Michl with the NYS Department of Health's Bureau of Environmental & Occupational Epidemiology provided an update on "A Retrospective Cohort Study of Mortality and Cancer Incidence Among New York State Female Farm Residents." Ying Wang, lead investigator on the study, was also present. One objective of this study is to determine if women residing on farms in NYS experience higher cancer incidence rates than the general female population for overall cancer and specific cancer. A similar study has been done of male farmers in NYS. Two years ago, the Ad Hoc group requested that such a study be done of women residing on farms; this study responds to that request.

Betsy discussed the fact that although farmers appear quite healthy in epidemiologic studies done to date and have a lower overall risk of cancer, studies also indicate that farmers may be at excess risk for certain cancers. She noted though, that those few existing studies on female farmers and farm residents found consistently lower incidences of lung and breast cancer. Betsy provided information on the study design (see also *The Ribbon*, Volume 3, Number 1, for background on epidemiologic study designs), how the data will be analyzed, and the strengths and limitations of this study. Results will be available within six months.

Pesticides in Surface Waters. Patrick Phillips from the US Geological Survey (USGS), Hudson River Basin National Water Quality Assessment (NAWQA) was next on the agenda. Patrick spoke on "Pesticides in Surface Waters of New York State, 1997." He described the findings from the USGS's 1997 work monitoring pesticides in state waters as required by the NYS Pesticide Reporting Law. Findings include:

• the most commonly detected pesticides were herbicides that are commonly applied to cornfields, including atrazine, metolachlor, and an atrazine degradation compound, deethylatrazine.

• all detected pesticides were at concentrations below federal health advisory or maximum contaminant levels; four insecticides and one herbicide exceeded applicable state criteria at ten sites (out of 64 tested).

• in general, concentrations varied considerably and were related to associated land use.

Patrick also highlighted the group's 1998 projects which include Long Island groundwater, a public water survey, and a Cayuga Lake study.

1st Annual Report, Pesticide Use and Sales. Margaret O'Neill of the NYS Department of Environmental Conservation (DEC) provided the group with an overview of the first annual pesticide report summary which was due by July 1, 1998. The actual data fills 4,859 pages in twelve separate reports, all of which is available through the DEC or Cornell's Pesticide Management Education Program (PMEP) world wide web sites (http://pmep.cce.cornell.edu/regulation/psur/annualreport1997/index.html). Margaret advised caution against the use of the data to draw specific conclusions about pesticide use in NYS at this time. One reason is

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

FACT SHEETS AVAILABLE

__*FS #1*--Phytoestrogens and Breast Cancer

__*FS #2*--DDT, DDE and the Risk of Breast Cancer

__*FS #3*--Understanding Breast Cancer Rates

__*FS #4* --Reducing Pesticide Exposure in the Home and Garden: Alternatives and Proper and Legal Use Resource Sheet

__*FS #5*--The Biology of Breast Cancer

__*FS #6*--Tumor Suppressor Genes—Guardians of Our Cells

__*FS #7A*--Reducing Potential Cancer Risks from Drinking Water--*Part I: Contaminant Sources and Drinking Water Standards*

__*FS #7B*--Reducing Potential Cancer Risks from Drinking Water--*Part II: Home Water Treatment Options*

__*FS #8*--Childhood Life Events and the Risk of Breast Cancer

__*FS #9*--Estrogen and Breast Cancer Risk: What Is The Relationship?

__*FS #10*--Estrogen and Breast Cancer Risk: What Factors Might Affect a Woman's Exposure to Estrogen?

__*FS #11*--Pesticides and Breast Cancer Risk, An Evaluation of Chlordane

__*FS #12*--Pesticides and Breast Cancer Risk, An Evaluation of Heptachlor

__*FS #13*--Alcohol and the Risk of Breast Cancer

__*FS #14*--Pesticides and Breast Cancer Risk, An Evaluation of 2,4-D

__*FS #15*--Pesticides and Breast Cancer Risk, An Evaluation of Lindane

__*FS #16*--Pesticides and Breast Cancer Risk, An Evaluation of Simazine

__*FS #17*--Pesticides and Breast Cancer Risk, An Evaluation of Cyanazine

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BCERF Critical Evaluations

Critical Evaluations on **2,4-D** and **lindane** are available on the BCERF web page as portable document files (pdf), and can be accessed on the BCERF web site at http://www.cfe.cornell.edu/bcerf/CE.list.html. **If you would like to order a hard copy indicate below and send your check payable to Cornell University to cover the costs for copying and mailing:**

__ Lindane Critical Evaluation ($3.00)

__ 2,4-D Critical Evaluation ($3.00)

—add me to your mailing list

—send me a copy of the BCERF Brochure

__remove me from your mailing list

that the data is only reflective of reports received through May 1, 1998; reports received after this date will be made available after December 1998. Also available on the DEC world wide web site is an Executive Summary (http://www.dec.state.ny.us/website/dshm/prl/exec.htm).

Health Research Science Board. Patricia Lowney, a Grant Specialist with the NYS Department of Health, reported on funding for breast cancer research in NYS. She began by describing the total amount of funds spent on breast cancer in NYS ($48 million) and then updated the group on the status of the tax check-off monies ($1.1 million) to be awarded for the first time, following the initiation of that program. Following the recent request for proposals, the Health Research Science Board has received 84 proposals, requesting a total of $3.9 million. A three panel merit review process is being implemented, and panels will be composed of 10-12 scientists and 3-4 advocates, all voting members. The group was interested to find out that no proposals were received pertaining to pesticide exposure.

Mark Your Calendars!!!

Ad Hoc Discussion Group meeting
Thursday, September 17, 1998
Large Conference Room (G10)
Biotechnology Building, Cornell University
Ithaca, NY
11:00am to 4:00pm

Ad Hoc Discussion Group meetings are open to any and all stakeholders to come together to discuss issues related to breast cancer and environmental risk factors.

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WHAT'S NEW "ON THE WEB"

http://www.cfe.cornell.edu/bcerf/

The coming year will see dramatic changes in the BCERF website, starting with the relaunch of the site with a new look and improved navigation.

The site's new features will include online access to BCERF's newsletter, *The Ribbon*. Users will be able to browse the newsletter online or download it in its original format. The newsletter pages will be able to be navigated by article title or by issue.

The site will also provide an archive of past minutes of Ad Hoc Discussion Group meetings, in addition to information about upcoming Ad Hoc meetings. The Ad Hoc Archive will contain publication quality files of the minutes (PDF), as well as text formatted versions.

Visitors to the new *Readers Forum* will be able to sign up electronically for email notification of the newest fact sheets and newsletters. Readers interested in notification of the publication of new Critical Evaluations will also be able to use the Forum to sign up for notification of their release.

Our online resources are consistently growing for both the scientist and the non-scientist.

Marie Stewart, BCERF "Webmaster"