The Ribbon

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

Volume 4, Number 2, Spring 1999

INDEX

Prostate Cancer: Rates and Possible Risk Factors
An Interview with Dr. Otis W. Brawley 1

US TOO International, Inc. 7

Research Commentary
Mammographic Densities and Breast Cancer 9

What's New on the Web 10

Prostate Cancer: Rates and Possible Risk Factors

An Interview with Dr. Otis W. Brawley

Otis W. Brawley is Director of the Office of Special Populations Research and Assistant Director, Office of Science Policy at the National Cancer Institute. He was previously in the Division of Cancer Prevention and Control (DCPC) at the National Cancer Institute. He also served as chief of the NCI intramural prostate cancer clinic.

Dr. Brawley is board certified in internal medicine and medical oncology. He has clinical privileges as an attending physician at the National Institutes of Health Clinical Center and the National Naval Medical Center (Bethesda Naval Hospital). He graduated from college and medical school at the University of Chicago and was an internal medicine resident at University Hospitals of Cleveland, Case Western Reserve University. Dr. Brawley came to the NCI in 1988 as fellow in medical oncology and joined the DCPC senior staff in 1990.

Dr. Brawley's research interests include the screening, epidemiology, diagnosis, prevention and treatment of prostate cancer. He has additional interests in the design of clinical trials, inclusion of minorities in trials and the availability of state-of-the-art health care to the socioeconomically disadvantaged.

To begin, please give us an idea of recent trends in prostate cancer incidence and mortality.

Throughout the 1950s and '60s there was relatively stable incidence and mortality of prostate cancer. Then, in the late 1970s the trend started going upward in incidence, although mortality stayed the same (see Figure 1).We have now figured out that incidence went up because of what we call TURP, or, transurethral resection of the prostate, for treatment of benign prostatic hyperplasia, a benign swelling of the prostate. More men getting prostates manipulated by surgery led to more prostate tissue being sent to pathologists, and pathologists were diagnosing more prostate cancer. It's not that there was more prostate cancer, it's that there was more diagnosis of prostate cancer.

The mortality rate in the '50s, '60s and '70s is essentially flat, but you do have this rising in incidence that started in the '70s and continued into the '80s. Then, in the late 1980s we have the advent of the PSA (Prostate Specific Antigen) screening test. Actually this is a test

Figure 1

that still has not been approved by the FDA for screening; it has been approved for diagnosis and for following men who have disease. But the test has been used for screening and that dramatically increased the incidence of diagnosed prostate cancer in the 1980s and early '90s.

We can't really say much about true incidence, but we can say a lot about diagnosed incidence. We can look at true incidence by looking at autopsies, and I'll talk about that in a moment. But diagnosed incidence did go up dramatically, then in 1992-1993 diagnosed incidence started going down again. A 'clearing out of the prevalences' probably explains that. This means that there is a population of men to be screened and after all of them have been screened once, there's not nearly as many to be screened. When mammography came out, we also had a transient increase in incidence, followed by a decline later on.

Mortality went up slightly in the early 1980s. We had dramatic rise in incidence with just this small rise in mortality. In the early 1990s mortality started going down slightly, but not down to the levels it was in the '60s and '70s.

Mortality rates also may not be true mortality rates: 'attribution bias' is the phrase we like to use. In some men who die, since we now have this test that diagnoses prostate cancer, we attribute the death to prostate cancer. But many of those same men's deaths would have been attributed to a heart attack twenty years ago. We still don't know how much attribution bias there is.

There are also some small declines in mortality in Europe where there is no screening. We like to look at geographic differences in incidence and that helps to tell us about relative incidence and the power of screening. In the US for example, if one looks at various sites in the state of Washington, the prostate cancer incidence rate is more than twice that of the state of Connecticut through much of the late '80s and early '90s, and that's primarily because there's a lot of screening in Washington and less in Connecticut. But the death rates in both states are very similar; indeed the death rate in Connecticut is slightly lower than the death rate in Washington, which is again pointing toward attribution bias.

You direct the Office of Special Populations Research of the National Cancer Institute (NCI). What determines your choices with regard to selection of populations to study, and what has your research revealed with regard to differences in prostate cancer risk?

Much of what we do is trying to figure out the most important questions that the Institute ought to be addressing, and most of the time, those questions are to be addressed by external people whom we fund. Eighty-plus percent of the NCI budget goes to institutions throughout the country to do cancer research. Much of what we do is agenda setting. We are very interested in prostate cancer primarily because that's what I did for 15 years before I had this job — I'm a prostate cancer physician. We have published a lot on prostate cancer,

but we are also very interested in breast cancer. We are very interested in the roles of race and ethnicity as they relate to cancer causation (see Figure 2), and how they relate to cancer treatment; we do a lot of 'patterns of care' studies. The patterns of care studies in prostate cancer have been used to tell us that there really are some significant issues in prostate cancer. We have a large number of people treated in one area versus another, but again, the same death rate.

Figure 2

What is an example of agenda-setting research?

We have a program that the office operates that requests groups of individuals, primarily community organizations, to apply for funding to work in collaboration with universities. This work would entail defining the questions that need to be addressed, and actually developing the research projects. One of the ways we are answering the question is by not answering the question — rather by enabling people out in the real world to answer the question — what kinds of research needs to be done? The research that is designed under this program is still going to have to go through peer review and meet certain standards to be funded. However, the program is designed to try to help community groups and others work with universities and people who are funded to do research already.

We've worked a great deal to establish the Breast Cancer Progress Review Group as well as the Prostate Cancer Progress Review Group. Those were both sponsored by the Office of Science Policy. We spent a great deal of time making sure special populations issues are dealt with in the reports of those groups.

See reports of these groups on the World Wide Web:

Defeating Prostate Cancer: Crucial Directions for Research
Report of the Prostate Cancer Progress Review Group
http://wwwosp.nci.nih.gov/planning/prg/toc.htm

Charting the Course: Priorities for Breast Cancer Research
Report of the Breast Cancer Progress Review Group
http://wwwosp.nci.nih.gov/planning/prg/bprgtableofcontents.htm

Can you give an overview of some of the important epidemiological studies that are currently in progress?

There's a large case-control study that is looking at men in China as well as black and white men in the US. It is a comparative epidemiological study to look at risk factors for prostate cancer; to look at what the lifestyle reasons may be for the difference between blacks and whites, and men from Asia. There's another, a smaller study that's looking at blacks and whites in the US, looking at environmental and lifestyle issues.

There are our larger screening studies, the Prostate, Lung, Colon and Ovarian Cancer Screening Study. This includes a randomized trial with the goal of answering the question, "does screening for prostate cancer save lives?" as well as looking at screening for other cancers.

Then there is the Prostate Cancer Prevention Trial, a study I helped to design, which is looking at the question of whether the drug finasteride decreases the incidence of prostate cancer. It's a drug that's already approved for treatment of BPH, benign prostatic hyperplasis. There's a lot of theory that it may prevent prostate cancer. The study is a randomized trial, so we are giving it to half the men for seven years, while the other half get a placebo. Our goal is to figure out if after seven years these men have a lower prevalence of prostate cancer. Slightly over 18,000 men spread over 222 sites in the US and Canada are included in this study.

Others include a study at Wayne State University in Detroit, where extramural investigators are examining early preneoplastic and malignant changes in the prostates of autopsied African American and White men who died of traumatic causes; in other words, looking at the true incidence of prostate cancer. At the University of North Carolina, a study on prostate cancer is assessing whether excess prostate cancer in African Americans is associated with lower intake of omega-3 fatty acids.

What would you say is similar, and what is different, about the progress we have made in understanding the risk factors for two diseases, breast cancer and prostate cancer?

We know a great deal more about risk factors for breast cancer than for prostate cancer. Your readers may be familiar with the data about women who have had a full term pregnancy before age thirty, data about age of first menstruation, even the data on fat women versus thin women. We don't know any risk factors for prostate cancer except being a male, being older (see Figure 3), and having a first degree relative with prostate cancer. And having a first degree relative with prostate cancer may actually be more correlated with diagnosis of prostate cancer versus having prostate cancer. A man with a brother or father with prostate cancer is more likely to get screened.

We maintain a list of what all the various organizations recommend about screening and the majority are actually against screening. In Europe they are much more conservative in their public health stance. One of the basic premises is that you don't do something until you know it works. There are five clinical trials underway in Europe to look at the issue of screening. But it's very difficult for a man to get screened in Europe. Mass screening is almost totally unheard of.

How does this compare to any difference in screening for breast cancer between the US and Europe?

Most countries in Europe are not screening women under the age of 50. However their compliance rates for screening women 50 or over are much higher than in the US. I think that is partly explained by more centralized medical care and partly by a different view of medicine in general. The whole culture towards medicine is different. But I think the centralized medical care as well as everyone having medical care is important. The one country where there is a lot of screening for women in their forties is Sweden. But you go to Denmark and you are not going to find much screening for women in their forties. However, women who are at perceived high risk do tend to get screened in their forties.

NCI has said that an analysis of its Prostate and Breast Cancer Review Groups reveals many important similarities in need from these two independent groups. What similarities in need do you see?

The main thing is that good research is the thing to be desired — not necessarily prostate cancer research or breast cancer research. Some of the findings from prostate cancer research have been amazingly important in breast cancer. For example, many of the people who ultimately isolated the estrogen receptor and the whole tamoxifen story were trained by Charlie Huggins at the University of Chicago. Charlie Huggins won the Nobel Prize for doing the first orcheectomy to treat prostate cancer. The money spent in his laboratory, which was called prostate cancer research in the '50s and '60s, trained the researchers who made one of the biggest breakthroughs in breast cancer research. Zolodex, which was designed for the treatment of prostate cancer, has been approved by the FDA for the

Figure 3

treatment of breast cancer. So here you have prostate cancer research benefiting breast cancer research twice.

Estramustine, which was from 1973 to 1995 the only non-hormonal chemotherapy approved for the treatment of metastatic prostate cancer, was designed in the '60s and early '70s as a 'designer' breast cancer drug. It was linking estrogen with nitrogen mustard with the idea that the estrogen would internalize the nitrogen mustard in a breast cancer cell so it could kill the breast cancer. That theory was flawed and it did not work in breast cancer. But the drug ended up being the only chemotherapy approved for the treatment of metastatic prostate cancer for almost 25 years. The Progress Review Groups found out that there are a lot of important links between breast and prostate cancer. They also found out some important genetic findings in breast cancer came out of research that almost anyone would call lung cancer research. What the Progress Review Groups found is that what we need is good research, more so than specifically prostate cancer research or breast cancer research.

Many dietary hypotheses are being explored for their possible role in breast cancer risk. Are there strong dietary hypotheses with regard to prostate cancer risk?

Absolutely. In the *Journal of the National Cancer Institut*e recently there is a review by Laurence Kolonel on the data between diet and prostate cancer (Laurence N. Kolonel, Abraham M. Y. Nomura, Robert V. Cooney, "Dietary Fat and Prostate Cancer: Current Status" JNCI, Vol. 91, No. 5, 414-428, March 3, 1999). Larry Kolonel is one of the people who has shown that if you study migrants from China or Japan to the US, those people in the US have higher prostate cancer rates than do people remaining in China or Japan. Most importantly, this was determined before people who migrated from Japan or China were likely to be exposed to PSA screening. It was before mass screening started that we realized that migrants have higher rates of prostate cancer, so that really implies that there is some kind of environmental or lifestyle factor that influences prostate cancer risk.

What might some of those environmental or lifestyle factors be?

Unfortunately the most that we can talk about right now is "might." Many people think that dietary fat may have something to do with prostate cancer risk. Some believe that it is animal fat as opposed to vegetable fat that increases risk. Some people are actually looking at whether it is actually not what they eat when they get to the US, but what they <u>don't</u> eat when they get to the US. So there's a lot of interest in soy products, especially genistein from soy and several flavanoids that are in soy products that may prevent or suppress prostate cancer.

Is this message getting out, and should it be?

It needs to be stressed that this is what we believe, this is not what we know for a fact yet. But I do see the message getting out a bit and it might be premature for this message.

And with breast cancer risk?

We can say that 5-9 fruits and vegetables a day seems to be correlated with a decreased incidence of a number of cancers; breast, prostate and colon among them. And that 5-9 fruits and vegetables can definitely be advocated because it decreases heart disease risk. I'm a great believer that we scientists should speak freely about what is known, what is not known, and what is believed.

One of BCERF's founding missions and ongoing projects is to explore a possible link between pesticide exposure and breast cancer risk. Is there work being done on this question for prostate cancer?

There's an epidemiologic study, the Agricultural Health Study, which looks at this issue. This is a prospective cohort study of licensed pesticide applicators, primarily farmers, and their spouses and children, that is being conducted in Iowa and North Carolina by NCI, NIEHS, and EPA. Detailed information is being collected on agricultural exposures and other risk factors. Cancer incidence and mortality, including that for stomach cancer and other cancers, will be evaluated. It appears, though, that the incidence and mortality of prostate cancer might be slightly lower among farmers.

In your group's report, "Defeating Prostate Cancer: Crucial Directions for Research," it says that "it may not be necessary to prevent prostate cancer initiation, but rather a more effective approach may be to focus on prevention of progression to more aggressive disease." Can you explain that a bit?

The answer to this question is linked to the autopsy studies. A large number of men who go to autopsy after death from trauma have prostate cancer. Subtract ten from the decade of life: 60% of men in their seventies,

50% of men in their sixties, 40% of men in their fifties, have prostate cancer on autopsy when they die of a non-cancer cause. The difference between those men and the men I take care of in my prostate cancer clinic is those men have small lesions of cancer, sometimes only one or two millimeters in size, whereas the men in my clinic have that same cancer but they will sometimes have large amounts. We can weigh it in grams or kilograms. If we can stop the influences that cause one of those small tumors to grow to a big tumor, we can save a man from getting prostate cancer diagnosed, and save him from treatment and prostate cancer death. Even if it's already a large tumor, if we can make it indolent and stall it out for a while, since we're dealing with men whose median age is seventy-one and there are competing causes of death, that's all we really need to be successful.

Where do you see the most promise for prostate cancer risk reduction?

I see the most promise in doing more clinical trials to find out the etiology and then some of the prevention. Two large clinical trials have already shown prevention of prostate cancer, for example the Finnish trial that looked at beta carotene and Vitamin E for lung cancer prevention. It actually found an increased incidence of lung cancer in people treated with beta carotene, but it had a serendipitous finding of a 30% decrease in prostate cancer among the people treated with Vitamin E. Because that was not one of the initial goals of the trial, we need a prospective trial to confirm it and we are going to do that. It was a two-by-two design with 28,000 people: a quarter got Vitamin E, a quarter got beta carotene, a quarter got both and a quarter got a double placebo. They were all male smokers in Finland, treated for 6-8 years. Since there is no screening in Finland, this is a 34% reduction in what I would call "real" prostate cancer, clinically-presenting prostate cancer.

The selenium study was a study looking at selenium and the prevention of skin cancer that again had a serendipitous finding of a reduction in the amount of prostate cancer in men treated with yeast selenium. But since neither of these was a prospective trial in which the initial hypothesis was that the intervention would prevent prostate cancer, both really need to be confirmed in prospective trials to make sure that there's not some kind of bias that we are just not smart enough to figure out. But both of those studies are very sound in my mind, and we are planning a study that will start next year. It will involve 32,000 men. Again, a two-by-two design, selenium, Vitamin E, both or placebo. I look at the dietary studies that are already going on, the finasteride study, and the Vitamin E and selenium study to try to figure out how we are going to prevent prostate cancer. I also look toward the screening studies here and in Europe to try to figure out if prostate cancer screening saves lives.

Do you have any thoughts on chemoprevention versus diet and lifestyle risk reduction or do you think both have promise?

Both have promise. We may actually find out that the reason some ethnicities don't tend to have a cancer and some do, is because their diet has chemoprevention already inside of it.

You have said that ultimately the cause of prostate cancer is likely to be a combination of genetic and environmental factors. Can you comment?

The black/white issue and genetic question always comes up. We have candidate genes for prostate cancer risk. My guess is that the genetics of prostate cancer involves several genes and several polymorphisms of genes, and distinguishing that is going to be very hard. It's going to be much messier than the genetic breast cancer story. I do think there's a genetic reason for many people to get prostate cancer: I think environment and genetics interact to cause these cancers, and here I'm telling you what I believe as opposed to what I know. But these are hypotheses that other people and I have generated and are the basis of a lot of the etiology research that's ongoing right now. I don't believe that there will be a black prostate cancer gene ultimately when this is all found out. I do believe there will be a prostate cancer gene of higher prevalence in blacks, just as sickle cell genes are of higher prevalence in blacks, or Tay Sachs genes are of high prevalence in Jews. But neither sickle cell nor Tay Sachs is exclusive to blacks or Jews. It does seem though that family history is more important than race history, and race frequently tracks with family. But I do believe there is a genetic basis for a lot of prostate cancer, probably all prostate cancer, but environmental influences are going to be important as well.

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

US TOO International, Inc. is an independent peer support organization. It was started by five men, each of whom had been diagnosed with and treated for prostate cancer and were interested in discussing their common problem with others. These men formed the original Board of Directors and held their first meeting in February of 1990. Since then, US TOO has grown to over 550 chapters throughout the United States, including chapters in other countries. The leaders and coordinators of these chapters, as well as the Board of Directors, all volunteer their time and services.

An US TOO support group is an excellent setting to keep abreast of the ever-changing field of prostate cancer. Speakers at US TOO meetings include urologists, oncologists, scientists, nutritionists and other health professionals dealing with prostate cancer on a daily basis. The support group is a good way to discuss possible clinical trials for which a patient may be eligible, as well as newly approved drugs, diagnostic techniques and treatments.

Many support group meetings include "rap" sessions in which patients and family members can discuss issues ranging from treatment side effects such as impotence and incontinence, to topics such as complementary medicines and diet, and new prostate cancer research studies. A new break-out group, *US TOO Partners*, holds additional, separate meetings of its own. It is designed to provide partners of survivors the opportunity to discuss issues they face themselves while dealing with their loved ones' disease. Prostate cancer is regarded as a family disease since it impacts the lives of patients' wives and other family members. They are encouraged to attend meetings not only to help the survivor, but to gain support for themselves.

Members of US TOO support groups increasingly are joining in the national survivors advocacy movement, especially promoting greater public funding support for prostate cancer research. To enhance this activity, US TOO and the National Prostate Cancer Coalition (NPCC) are working together on the US TOO Advocacy Program, an innovative organizing project designed to enhance the advocacy skills of prostate cancer survivors across the country. This exciting program builds on the vast network of survivor support groups of US TOO and the organizing, training, and grassroots activist skills of the NPCC staff and consultants.

The advocacy program recognizes that men can and will be the most effective public advocates on issues directly affecting their health if given sufficient information, training and direction. The overall goal of the US TOO Advocacy Program is to identify, enlist and support a national team of prostate cancer advocates comprised of US TOO chapter members. US TOO Chapter Advocacy Coordinators serve as the key point of contact within the support group on federal and state legislation and other policy matters.

US TOO publishes two publications, *The US TOO Prostate Cancer Communicator*, a quarterly newsletter, and *The US TOO Hot Sheet*, a monthly publication distributed to members at chapter meetings. Publications focus on clinical trials, scientific advances, and events such as regional symposia for professionals, patients and families. For a referral to a local chapter or to find out more about the organization, call the US TOO headquarters office in Hinsdale, Illinois at 1-800-808-7866. A listing of chapters nationwide can also be found on the US TOO web site at http://www.ustoo.com.

Article submitted by Sue Duy, Administrative Director, US TOO International, Inc.

BCERF's First Electronic Update

BCERF is proud to announce the beginning of our electronic notification list, the e-Update. The list is designed to inform interested readers of the BCERF website about new resources and features. If you would like to receive the quarterly e-Update join us on-line at <http://www.cfe.cornell.edu/bcerf/response.t>.

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

FACT SHEETS AVAILABLE

__*FS #1*--Phytoestrogens and Breast Cancer (no longer available in printed form. Accessible on the BCERF web site)

__*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

__*FS #18*--Fruits and Vegetables and the Risk of Breast Cancer

__*FS #19*--Exercise and the Risk of Breast Cancer

__*FS #20*--Pesticides and Breast Cancer Risk, An Evaluation of Dichlorvos

__*FS #21*--Avoiding Exposure to Household Pesticides: Protective Clothing

__*FS #22*--Safe Use and Storage of Hazardous Household Products

__*FS #23*--Pesticides and Breast Cancer Risk, An Evaluation of Atrazine

__*FS #24*--Consumer Concerns About Pesticides in Food

__*FS #25*--Pesticide Residue Monitoring and Food Safety

__*FS #26*--Pesticides and Breast Cancer Risk, An Evaluation of Chlorpyrifos

Cornell University
Program on Breast Cancer and Environmental Risk Factors in New York State
110 Rice Hall, Cornell University
Ithaca, NY 14853-5601
Phone: (607) 254-2893; FAX: (607) 255-8207
E-Mail: breastcancer@cornell.edu.

NAME_____

Address_____

_____

_____

Telephone _____ Fax _____ Email _____

BCERF Critical Evaluations

Critical Evaluations 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/. **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:**

__ #1 — 2,4-D ($3.00)
__ #2 — Lindane ($3.00)
__ #3 — Heptachlor and Heptachlor Expoxide ($3.00)
__ #4 — Chlordane ($3.00)
__ #5 — Simazine ($3.00)
__ #6 — Cyanazine ($3.00)
__ #7 — Dichlorvos ($3.00)

—add me to your mailing list

—send me a copy of the BCERF Brochure

__remove me from your mailing list

Research Commentary

Mammographic Densities and Breast Cancer Risk

Norman F. Boyd, Gina A. Lockwood, Jeff W. Byng, David L. Tritchler and Martin J. Yaffe. Cancer Epidemiology, Biomarkers & Prevention, Volume 7, 1133-1144, December 1998.

Mammography may provide women with more information than simply detecting potential/suspicious growths and tumors. The overall x-ray image of the female breast obtained in a mammogram is different for each individual woman due to differences in the relative amounts of fat, connective and epithelial tissue. These different radiological patterns created by variations in the relative amounts of these tissues, referred to as the parenchymal patterns of the breast, have been known to be associated with risk of breast cancer. Early studies that observed this association relied on a subjective, qualitatively based classification of breast parenchyma in terms of four distinct patterns from a radiologically lucent pattern (fat) that appears dark on a mammogram, to a more radiologically dense pattern (connective and epithelial tissue) which appears light on a mammogram. Subsequently, researchers developed quantitative methods to assess the proportion of the breast occupied by radiologically dense tissue based on visual examination, planimetry and digitized images with computer-assisted methods to measure breast density, considerably improving on measurement techniques and methods.

In this manuscript, the authors present a comprehensive and complete review and summary of research conducted between 1976 and 1997 on the relationship between breast density and the risk for breast cancer. Eight out of the nine studies (five conventional case-control studies and four nested case-control studies) conducted to date using quantitative assessment of breast density reported a dose-response relationship or statistically significant trend of increasing risk of breast cancer across categories of density analyzed in each study. Radiologically dense breast tissue is not only reported to be associated with a large increase in the relative risk (RR) of breast cancer but also appears to be present in a substantial proportion of subjects with the disease. The authors estimate that 28-33% of breast cancer cases may be attributable to dense tissue in >50% of the breast. They further propose that dense breast tissue indicates proliferation of the breast epithelium and stroma in response to growth factors induced by circulating levels of sex hormones.

There are however, several caveats regarding this potentially important finding. The first plausible argument that calls into question the association of breast density and risk is the "masking" effect of breast density in the detection of tumors. Breast cancer is easiest to detect by mammography in breast tissue with radiolucent parenchyma and most difficult to detect in breast tissue with dense parenchyma. Therefore it appears likely that more cancers may not be detected at first examination in subjects with dense breast tissue and will be detected subsequently. However, very similar estimates of risk obtained in case-control studies (mammograms taken at diagnosis) and cohort studies (mammogram taken at baseline entry to cohort) together with the persistence of risk over extended follow-up in cohort studies, suggests that "masking" does not distort estimates of risk and may not pose a problem in these studies. Furthermore, research on a cohort of subjects regularly examined over an extended period of time, has shown that any effect of "masking" on risk estimates will be small and short lived because cancers missed on one examination will eventually be detected at a later examination.

Mammographic density has been shown to be associated with several other risk factors for breast cancer. Most of these relationships are consistent with findings from observational studies on these other risk factors such as age, body weight, family history, parity etc. However certain anomalies remain and further investigation of these inconsistencies is warranted. For example, there is an apparent paradox in that breast cancer incidence increases with age, being higher in postmenopausal versus premenopausal women, yet dense breast tissue is more common before rather than after menopause. Thus, the decline in density with increasing age suggests that it is density at a given age, rather than density *per se*, that is the relevant measure with respect to breast cancer. The authors correctly point out that studies of density as a risk factor must therefore compare women of the same age. Another important risk factor for breast cancer is body size. Body weight and body mass index have been repeatedly shown to be inversely associated with breast density. This is consistent with the inverse effect of body size with premenopausal breast cancer but is at odds with the observation that obesity is a risk factor for postmenopausal breast cancer. Similar findings on family history and density are equivocal and do not indicate a clear relationship.

Very few studies have been conducted to examine the relationship between breast density and readily

modifiable risk factors such as nutrition and exercise. The few studies that have been reported suggest that diet, particularly the intakes of total and saturated fat, may have a causal role to play in the etiology of breast density. The authors suggest that breast density is an independent risk factor for breast cancer as it remains associated with risk after adjusting for the effects of other risk factors. However, based on arguments presented in this review and current understanding of the etiology of breast cancer, breast density is better viewed as an intermediary biological marker for disease propensity. For the immediate future, radiological characteristics of the breast might be used to determine the length of the interval between mammographic screenings, and breast density can be effectively studied as an outcome measure or proxy for breast cancer risk. This report clearly underscores the need for further research to identify the dietary and hormonal factors that modulate and influence breast density and establish the biological and nutritional mechanisms that influence mammographic density.

Prepared by Banoo Parpia, Senior Research Associate, Division of Nutritional Sciences, Cornell University

WHAT'S NEW "ON THE WEB"
http://www.cfe.cornell.edu/bcerf/

The close of winter and the arrival of warmer weather saw a flurry of additions to the BCERF website. Browsers will see that nearly every category has increased in what it offers. *Critical Evaluations* for Atrazine and Dichlorvos were posted for their respective 30-day comment periods. Three new fact sheets were added to the website in April. The new fact sheets cover consumer safety concerns, pesticides and food safety, and the pesticide chlorpyrifos. Our collection of searchable references in the Environmental Risk Factor Database grew to include over 3300 entries. Also added to the website are three new bibliographies for our critical evaluations, including: Atrazine, Chlorpyrifos, and Diazinon. Updates and new information sources are sprouting rapidly, so come take a look and see how we have grown.

Marie Stewart, BCERF "Webmaster"

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

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