National Cancer Institute

Family Research Matters

A Newsletter for Family Members of the NCI Familial Breast-Ovarian Cancer Studies Registry

Winter 2000/2001

New Clinical Cancer Genetics Research Program Opens at NCI

The recent dramatic discoveries of the genes that cause some of the inherited forms of cancer have created challenges related to the care of people who have mutations (alterations) in these genes:

- When is the genetic test for mutations in a given gene ready to be applied in routine clinical practice?
- What is the best way to examine and monitor people with mutations for early signs of cancer?
- How can we act to reduce the risk of cancer among people at increased genetic risk?
- How can we reduce the stress, anxiety and disruption of daily life that go with genetic risk assessment and genetic testing?
- How can we insure that members of high-risk families can take advantage of this new knowledge without placing themselves at risk of genetic discrimination?

The National Cancer Institute has created a new research program to address these urgent issues. Known as the **C**linical **G**enetics **B**ranch (**CGB**), its mission is to insure that members of high-risk families and their health care providers have the information they need to make effective health care decisions.

Returning to NCI to lead this effort is medical oncologist and cancer geneticist Mark H. Greene, M. D. Many of you

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NATIONAL CANCER INSTITUTE

Recent Advances in Hereditary Breast/Ovarian Cancer Research

In the 3 years since our last issue of "Familial Breast-Ovarian Cancer News," new research in this field has moved forward at a rapid pace. The discovery of the BRCA1 and BRCA2 genes led to important new findings that promise to improve our ability to enhance both quality of life today and hope for tomorrow among the members of families with **h**ereditary **b**reast/**o**varian **c**ancer (**HBOC**). **None of these studies would have been possible without the cooperation, participation, dedication and sacrifice of**

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may remember Dr. Greene from his service as leader of NCI's Family Studies Program from the mid 1970s to the mid-1980s. That program became the **G**enetic **E**pidemiology **B**ranch (**GEB**), now headed by Dr. Peggy Tucker. He has spent the past 14 years as a practicing cancer specialist. For the last 5 years, Dr. Greene has directed the Mayo Foundation's Familial Cancer Program. It is with great energy, enthusiasm and broad experience that he has taken on the challenge of building this new Program.

Joining him in this effort is a rapidly growing staff of experienced and dedicated cancer genetics researchers, including:

- *Ruthann Giusti, M.D., M.P.H.*, Staff Clinician, a medical oncologist who is leading CGB's first new project, a study of new breast imaging techniques among young women from families with BRCA1/2 mutations;
- *Jennifer T. Loud, M.S.N., C.R.N.P.*, Nurse Cancer Genetics Research Nurse and Oncology Nurse Practitioner, who will coordinate nursing care and nursing research activities for CGB;
- *June A. Peters, M.S.*, Genetic Counselor, who will provide genetic counseling services to our study participants and who will take the lead in developing research projects related to genetic counseling issues;
- *Nancy Weissman, M.S.S.W.*, Licensed Clinical Social Worker, who will provide psychosocial support to, and evaluate the impact of genetic testing upon, the members of our families with hereditary breast/ovarian cancer; and
- *Ron Kase, B.S.N., M.B.A.*, and *Terri Giambarresi, B.S.N.*, research nurses well known to you all from their years of work on the hereditary breast/ovarian cancer project, who will continue to play a vital role in this study

[Please visit CGB's Web site for more detailed biographical information about our staff: http://www-dceg.ims.nci.nih.gov/hgp/cgb/index.htm

Of course, the researchers in CGB and in GEB will work closely together in all the studies of families prone to hereditary breast/ovarian cancer. Dr. Jeffery Struewing, who has led both the clinical and the lab research effort for the past 5 years, has moved into full-time lab work. He continues to devote his energy and expertise on lab research focussed on how BRCA1/2 actually work to produce cancer. Dr. Struewing will continue to be closely involved in this project, sharing the knowledge and expertise he has gained from the extensive work he has done with members of these families. Direction of the ongoing clinical follow-up and future research studies of the breast/ovarian families has shifted to Dr. Greene and the staff of CGB.

CGB has dedicated itself to finding better ways to reduce the burden of cancer in families who have mutations in BRCA1 and BRCA2. We look forward to working in partnership with you, as we continue NCI's effort to advance our understanding of hereditary breast/ovarian cancer.

Pictured in front row: Ruthann Giusti, Nancy Weissman, Peggy Tucker, Mark Greene
Back row: Ron Kase, June Peters, Jennifer Loud. (*Not pictured:* Jeffery Struewing, Terri Giambarresi)

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families at high risk, like yours. As a team, we really **can** make a difference, reducing the chance that families at increased risk will experience the pain and loss of loved ones from breast and ovarian cancer.

The following list provides a thumbnail sketch of some of the more recent developments that may be of interest to you:

- **First Publication from the NCI HBOC Education/Counseling Study Appears in Print!** Many of you are participating in the **N**ational **I**nstitutes of **H**ealth (**NIH**) Study of Education and Counseling for HBOC family members being conducted by Barb Biesecker and Dr. Jeff Struewing. The purpose of this study is to identify factors affecting the decision to get genetic testing in high-risk families. Nearly 600 letters of invitation were mailed out. In the first report to come from this study, we found that 80% of the 292 study participants who were evaluated by NCI elected to undergo genetic testing. Men and women were about equally likely to be tested, although folks who were older (above age 40) were more likely to choose testing than were younger family members. Based on questionnaire information, those who might be considered as "less optimistic" or as coming from families that were "more cohesive" (closer) were also more likely to choose testing. Information of this type may help health care providers learn who is most likely to benefit from BRCA1/2 testing within HBOC families. Further details can be found in the copy of this article that is included with the Newsletter. There will be more reports to come from this study, as follow-up and analysis continue. Our heartfelt thanks to all of you who are participating in this project, for helping to move the field forward.
{BB Biesecker et al. Psychosocial factors predicting BRCA1/BRCA2 testing decisions in members of hereditary breast and ovarian cancer families. *Am J Med Genet* 2000; 93:257-263}

- **Prophylactic (Preventive) Mastectomy Reduces the Risk of Breast Cancer**
Investigators at the Mayo Clinic studied 609 women with a family history of breast cancer who had undergone preventive removal of the breasts in an effort to avoid developing breast cancer. They observed approximately *90%* fewer breast cancers than expected, thereby providing the first real evidence that this surgical procedure truly **does** reduce the risk of breast cancer in women at high risk. [Risk is not completely eliminated because the surgery is unable to remove 100% of the breast tissue.]
{LC Hartmann et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *New Engl J Med* 1999; 340:77-84}

- **Prophylactic (Preventive) Oophorectomy May Reduce the Risk of Breast Cancer**
It is widely believed that a woman's risk of breast cancer increases as the amount of estrogen to which she is exposed increases. If that is true, then one might predict that when HBOC family members undergo preventive removal of the ovaries [to reduce their risk of *ovarian* cancer], their risk of *breast* cancer might decline as well, since the ovaries produce much of the body's estrogen. A recent report provides the first evidence that this may be true: the risk of breast cancer among BRCA1 mutation carriers was cut *in half* (i.e., reduced by 50%) among women who underwent prophylactic oophorectomy. This decrease in breast cancer risk becomes another important factor to consider as women wrestle with the decision regarding preventive removal of the ovaries.
{TR Rebbeck et al. Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. *J Natl Cancer Inst* 1999; 91:1475-1479}

- **Oral Contraceptives May Reduce the Risk of Ovarian Cancer**
It is well-known that the risk of ovarian cancer is reduced by about 50% (i.e., decreased by

half) among women from the *general population* who take oral contraceptives. The first report has now appeared which suggests that this same protective effect may be seen among women who have BRCA1/2 mutations. A study in HBOC families with known mutations demonstrated a similar 50% reduction in ovarian cancer risk. This suggests that the use of birth control pills may be a valuable *non-surgical* approach to helping women from families at high risk reduce their ovarian cancer risk. A note of caution: this is the only study so far to suggest that oral contraceptives may be useful in this setting. Other studies are currently underway, seeking to confirm this finding.
{SA Narod et al. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. *N Engl J Med* 1998; 339:424-428}

- **?? New Breast Cancer Gene Located ??**
A significant number of breast/ovarian cancer families do not have an identifiable mutation in either BRCA1 or BRCA2, including some of the families in our study. The basis for their cancer risk is unknown. Researchers from the NIH National Human Genome Research Institute and from Scandinavia performed a detailed study of 77 HBOC families without detectable mutations in BRCA1 or BRCA2. They identified a region on chromosome 13 which may be the location of a third major breast cancer gene. This is an important step towards actually identifying the gene, which has not yet been done. This may be a vital clue to the genetic basis for cancer in HBOC families which do not have mutations in BRCA1/2.
{T Kainu et al. Somatic deletions in hereditary breast cancers implicate 13q21 as a putative novel breast cancer susceptibility locus. *Proc Natl Acad Sci* 2000; 97:9603-9608}

Is Prophylactic Oophorectomy (PO) A Viable Option?

At present there are two **o**varian **c**ancer (**OC**) risk reduction techniques that are commonly discussed with women at increased genetic risk: oral contraceptives (birth control pills) and preventive removal of the ovaries, called **p**rophylactic bilateral **o**ophorectomy (**PO**).

To what extent does PO reduce ovarian cancer risk? Almost certainly, PO does make it much less likely that ovarian cancer will occur but, rarely, women who have undergone preventive removal of the ovaries develop an illness which resembles ovarian cancer known as **p**rimary **p**eritoneal **c**arcinomatosis (**PPC**). [This observation was made originally by NCI Family Studies investigators in 1982.] PPC occurs in women whose ovaries seem normal, and is thought to arise from other intra-abdominal tissues that are related to the ovaries. The existence of this condition makes it difficult to assure women who choose to have their ovaries removed that the operation will be completely protective against "ovarian cancer."

How common is PPC and how does PO affect quality of life in those women who choose to have their ovaries removed before menopause would normally occur? The answers to these important questions are not known at present. In order to address these issues, the CGB is preparing to launch a national study of a large group of women at increased genetic risk of ovarian cancer who are considering PO. This information should prove very helpful to women who are struggling with the complicated decision regarding prophylactic oophorectomy. If you are considering PO to reduce your risk of ovarian cancer, you may be eligible to participate in this study. You will hear more about this project in future mailings from us.

Menopause, Estrogen and Hormone Replacement Therapy

Another option (in addition to estrogen replacement therapy or hormone replacement therapy) for high-risk women experiencing menopausal complications is now available. Scientists have developed a new class of medications called "**SERM**s" (**S**elective **E**strogen **R**eceptor **M**odulators). These drugs have *both* estrogen-like effects and estrogen-blocking effects. The first of these medications, *tamoxifen*, was shown in 1999 to reduce the risk of breast cancer among women who are at increased breast cancer risk. The effect of tamoxifen is not yet clear in women with known BRCA1/2 mutations. A new study (known as the "STAR Trial") is now underway comparing, in post-menopausal women, the cancer-preventing activity of tamoxifen to a newer SERM called *raloxifene*. It is hoped that the side effects associated with raloxifene will be fewer and less bothersome than those seen following tamoxifen. Dr. JoAnne Zujewski of the NCI is conducting a special pilot study now underway here in Bethesda, which is studying the use of raloxifene in *premenopausal* women. Please let us know if you would like more information about this important project. You may be eligible to participate. Scientists are optimistic that these and other studies will lead to a variety of new options for cancer risk reduction from which persons at increased genetic risk can choose.

Help for Hot Flashes!

One hopeful note to those experiencing hot flashes: recent research suggests that small doses of antidepressants may be a new, non-hormonal way of controlling hot flashes. The medications studied are from the newest class of anti-depressants known as **SSRI**s (**s**elective **s**erotonin **r**euptake **i**nhibitors), which are particularly well tolerated. In a recent study from the Mayo Clinic, over 60% of the more than 200 women taking one of these medications experienced a significant decrease in the frequency and severity of hot flashes. In this study, side effects were minimal, as the dose used was only half of the usual amount needed to relieve depression. Scientists are hopeful that this class of medications may offer an effective short-term alternative for women who do not want to take hormones for menopausal symptoms, although decreasing the long-term effects of loss of estrogen remains a challenge for post-menopausal women.

[CL Loprinzi et al. Venlafaxine alleviates hot flashes: an NCCTG trial. *Proc ASCO* 2000;19:2a (abstract 4)]

Are BRCA1 and BRCA2 Linked to Prostate Cancer?

BRCA research has focused mainly on understanding the risk of breast and ovarian cancer in women who have altered BRCA1 or BRCA2 genes. It was, after all, the increased occurrence of breast and ovarian cancer within high-risk families which first led to the identification of the BRCA1 and BRCA2 genes. However, there are some data to suggest that BRCA1 and BRCA2 may be linked to prostate cancer as well. The Breast Cancer Linkage Consortium, an international group of investigators (which includes the NCI) has reported a modest increase in prostate cancer risk among those with an altered BRCA1[1] or BRCA2 gene[2]. *Dr. Jeff Struewing* from our group has

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[1] D Ford et al. Risks of cancer in BRCA1-mutation carriers. *Lancet* 1994; 343:692-95

[2] The Breast Cancer Linkage Consortium: Cancer risks in BRCA2 mutation carriers. *J Natl Cancer Inst* 1999; 91:1310-6

BRCAI and BRCA2...continued from page 5

studied cancers occurring in families drawn from a large group of Ashkenazi Jewish volunteers in the Washington, DC area. In this study, an excess of prostate cancer was also found.[3] However, other studies have raised doubts as to whether this association is real, and there are many questions which remain regarding the risk of and behavior of prostate cancer in men who carry a BRCA1 or BRCA2 mutation.

To try to determine with certainty whether prostate cancer truly is a part of the BRCA1/2 syndromes, *Dr. Ruthann Giusto* of CGB is conducting a detailed genetic and pathology study of 1000 Israeli men with this cancer. If the link between prostate cancer and BRCA1/2 mutations is confirmed, this will lead to a major new screening and intervention study focussing on the *men* from our hereditary breast/ovarian families. In the meanwhile, screening for prostate cancer in HBOC families is of uncertain benefit. Until there is more information about the risks and benefits of prostate cancer screening, in this setting, men who carry an altered BRCA gene should discuss the pros and cons with their doctor.

[3] J Struewing et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *New Engl J Med* 1997; 336:1401-8

Early Detection of Breast Cancer in Women at High Risk

Breast cancer in women who carry an altered BRCA1 or 2 gene often occurs at an early age. Many of these women will develop breast cancer before the age of fifty. Current recommendations for breast cancer screening include monthly breast self exam, annual or semi-annual breast physical exam, and annual mammography, beginning at 25 to 35 years of age. Compared with older women, mammography is less effective in detecting early breast cancers in young women, because they normally have very dense breast tissue which can interfere with cancer detection. There has been recent interest in studying the use of **m**agnetic **r**esonance **i**maging (**MRI**) to screen young women who are at high risk of developing breast cancer. MRI is an imaging technique which uses a strong magnetic field (instead of x-rays) to create a picture of the breast, and may produce a clearer view of the breast in young women without radiation exposure. In one recent study of high-risk women, MRI did detect some cancers that were not found by screening with mammography and ultrasound and did not appear more likely to give "false positive results."[4] [A "false positive"

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Future Plans

- *Dr. Mark H. Greene* is developing a new, national multi-center study of women who are considering prophylactic oophorectomy to reduce their genetic risk of ovarian cancer. The goal of the study is to develop additional information about what happens to women who choose preventive removal of the ovaries as well as those who choose to keep their ovaries, so that women and their health care providers can make an informed decision about the risks and benefits of this risk reduction strategy.

- Because the life experience of individuals from families with cancer susceptibility genes extends beyond cancer and its treatment, CGB's research program will include studies of genetic counseling, behavioral, psychosocial and nursing issues. The genetic counseling studies will be spearheaded by *June Peters*. *Jennifer Loud* will lead the effort to develop nursing research and preventive practices studies, and psychosocial studies will be led by *Nancy Weissman*.

If you would like additional information about these studies, you can contact *Terri Giambarresi* at 1-800-518-8474.

[4] CK Kuhl et al. Breast MR imaging screening in 192 women proved or suspected to be carriers of a breast cancer susceptibility gene: preliminary results. *Radiology* 2000; 215:267-79

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occurs when a test suggests that there is an abnormality, but additional testing finds no evidence of an abnormality.]

Dr. Ruthann Giusti is launching a new breast and ovarian cancer screening study at NCI using magnetic resonance imaging *(MRI) breast screening* and **p**ositron **e**mission **t**omography *(***PET** *)* along with mammography in young women from families with identified BRCA1 and BRCA2 mutations. It is hoped that these imaging techniques will improve our ability to find early breast cancers in mutation carriers. A new FDA-approved procedure, *"breast duct lavage,"* will be used to wash cells from the breast milk ducts (where breast cancers first arise) to determine if regular screening for changes in these cells may lead to early cancer detection or identify women at highest risk of developing breast cancer. This will be the first major, new clinical study of hereditary breast/ovarian cancer to be undertaken by the Clinical Genetics Branch. You will be hearing more about this project when it is ready to start enrolling participants.

Living with Your Genes: Nature and Nurture

Several studies (two of which are listed below) have addressed the issue of genetic risk ("nature") and environmental/lifestyle risk ("nurture") as causes of cancer. There is a growing concern that the excitement created by new genetic discoveries has resulted in people concluding that genes are the only thing that matter when it comes to determining one's risk of cancer. Some studies have even suggested that persons at increased genetic risk of cancer may be ignoring environmental or lifestyle cancer risks. While the way in which lifestyle choices affects cancer risk is still not completely understood, a generally healthy lifestyle is associated with significant improvement in overall health, and *may* reduce the risk of developing cancer as well. So, there IS more to your cancer risk than the information in your genes. A healthy lifestyle matters!

What lifestyle modifications are we talking about? Reasonable, general health maintenance recommendations include:

- Stop smoking
- Eat a well-balanced diet with modest levels of fat and 5 portions of fruits and vegetables each day
- Maintain a healthy body weight
- AVOID ALL TOBACCO PRODUCTS
- Exercise regularly (30 minutes, 3 to 4 times weekly)
- Limit alcohol to no more than 1 drink per day
- Use sunscreen lotion when out in the sun
- **STOP SMOKING,** and
- Remember to use your seat belt!!

Achieving these goals may not be easy, but they are good health choices for everyone.

Other lifestyle factors are statistically associated with lower risks of breast and/or ovarian cancer. These include:

- Having a baby before age 30
- Breast feeding after giving birth, and
- Taking birth control pills (which are associated with a lower risk of ovarian cancer and little, if any, risk of breast cancer)

Acting on information about these last three risk factors is more complicated than considering the lifestyle changes in the first half of the list. Each woman must consider how best to make use of this information and, with the help of her health care provider and people close to her, make her decisions on an individual basis.

Recent articles about "nature" and "nurture" that may be of interest to you:

- K Emmons et al. Behavioral risk factors among women presenting for genetic testing. *Cancer Epidemiol Biomarkers Prev* 2000; 9:89-94

- P Lichtenstein et al. Environmental and heritable factors in the causation of cancer. *New Engl J Med* 2000, 343:78-85

Resources and Information

Did you know that...

- The National Cancer Institute (NCI) provides cancer information to the public at no charge. Call **1-800-4-CANCER** to speak to an information specialist about any cancer related question, or to order such free booklets as ***What You Need to Know About Ovarian Cancer*** and ***Understanding Breast Cancer.*** You can also view these booklets online and get other useful information on cancer, resources and clinical trials at NCI's educational Web site: ***http://cancernet.nci.nih.gov***

- Cancer genetics information is available at NCI's Web site listed above, and at the University of Pennsylvania's Web site at: ***http://cancer.med.upenn.edu/causeprevent/genetics*** . Northwestern University's site at: ***http://www.cancergenetics.org*** also has extensive information on genetics.

- ***Genetic Testing for Breast Cancer Risk: It's Your Choice*** is available both as a videotape and booklet. Produced by the National Action Plan on Breast Cancer (NAPBC) and the NCI, it is designed to explore the issues related to genetic testing with those who think they may have a genetic susceptibility to breast cancer, and to describe the decision-making process involved when deciding to have or not have testing. The videotape version features women discussing their own experiences and feelings regarding testing, and is narrated by ABC commentator Cokie Roberts. For a free copy, call 1-800-4-CANCER.

- The comprehensive resource guide ***A Helping Hand*** is now available at no charge both online and as a brochure. Produced by Cancer Care, Inc., an organization dedicated to providing emotional support, information and practical help to people with cancer and their loved ones, the booklet offers information on transportation services, financial assistance, home care, support groups and so on, and describes specifically where to go to find this help. Cancer Care also provides telephone counseling, some financial assistance and educational materials. Its Web site address is ***http://www.cancercare.org***, and its telephone number is 1-800-813-HOPE (4673).

- ***The Cancer Survival Toolbox,*** produced by the National Coalition for Cancer Survivorship, the Oncology Nursing Society and the Association of Oncology Social Work, is a self-learning audio program that covers such important topics as communication with your medical team, finding information, solving problems and standing up for your rights. It is designed for people who are newly diagnosed with cancer, but the topics covered will help anyone at any stage of the illness who is facing difficult challenges and hard decisions. The Toolbox is available at no cost by calling 1-877-TOOLS-4-U.

These are but a sample of the information resources you can turn to as you gather what you need to know to master the complicated issues faced by you and your family. Let us know which you find useful, and which you do not. If you find a new one, tell us about it so that we can pass the word along to other study participants in the next Newsletter.

Glossary

BRCA1 and BRCA2 (**BR**east **CA**ncer genes numbers **1** and **2**) are two genes involved in cell growth. When mutated, they increase the risk of developing breast, ovarian and perhaps other cancers.

Magnetic Resonance Imaging (MRI) is a way of obtaining a picture or image of an organ using magnetic fields rather than x-rays.

Mutations are changes or alterations in genes that prevent the gene from working properly. Some mutations, called "germline," are inherited from parents and may be transmitted from one generation to the next, while others, called "somatic," occur only in one organ and are not passed on.

Primary Peritoneal Carcinomatosis (PPC) is a cancer that looks and behaves like ovarian cancer in women whose ovaries seem to be normal. It is thought to arise from the lining of the abdominal cavity where the ovaries, uterus, kidneys, liver and other organs are located.

Prophylactic Mastectomy (PM) is the removal of one or both breasts prior to any signs of cancer for the purpose of preventing breast cancer.

Prophylactic Oophorectomy (PO) is the removal of both ovaries and the fallopian tubes for the purpose of preventing ovarian cancer.

Selective Estrogen Receptor Modulators (SERMs) are medications that have both estrogen-like and estrogen-blocking effects. They are used to decrease the risk of developing breast cancer and other illnesses such as osteoporosis (thin bones) and perhaps heart disease. The two best-known SERMs are *tamoxifen* (brand name: Nolvadex) and *raloxifene* (brand name: Evista).