Collaborative Studies of *BRCA1/2* Mutation Carriers: PROSE and MAGIC

January 2007 Newsletter

This has been a productive year for our research collaborations. This newsletter is being sent to update you on our progress and plans for the PROSE and MAGIC research studies.

DATA UPDATE

DATA AND BIOSAMPLE COLLECTION

Our data collection as of November 30, 2006 is provided in the following table. Please contact Tara (tfriebel@mail.med.upenn.edu) if your center's numbers look incorrect, or if you have additional data/DNA to submit. Also, if you are currently participating in PROSE, and are interested in participating MAGIC as well, please contact us.

Center ID	PI	Study	Data Received *	DNA Received**	Data last updated
Austria	Wagner	PROSE,MAGIC	296	283	3/29/2006
Baylor-Houston	Plon	PROSE,MAGIC	21	0	4/15/2002
Baylor-Dallas	Blum	PROSE,MAGIC	22	15	5/23/2006
Beth Israel	Tung	PROSE,MAGIC	65	36	11/13/2006
City of Hope	Weitzel	PROSE,MAGIC	84	119	1/26/2006
Creighton	Lynch	PROSE,MAGIC	290	263	11/8/2006
Dana Farber	Garber	PROSE,MAGIC	281	171	11/6/2006
Duke	Schildkraut	PROSE,MAGIC	41	0	1/1/2002
Evanston N'western	Rubinstein	PROSE,MAGIC	71	57	9/13/2006
Fox Chase	Daly	PROSE,MAGIC	117	71	10/5/2006
kConFab	Trench	PROSE,MAGIC	815	815	10/6/2006
UCLA	Ganz	PROSE,MAGIC	63	63	8/3/2006
Georgetown	Isaacs	PROSE,MAGIC	122	173	8/24/2006
Mayo	Couch/Hartmann	PROSE,MAGIC	118	104	7/6/2006
NKI	Van 't Veer	PROSE	127	NA	11/1/2002
Penn	Domchek/Nathanson/Rebbeck	PROSE,MAGIC	435	418	9/1/2006
Marsden	Eeles	PROSE	88	NA	7/26/2006
St. Mary's	Evans	PROSE	313	NA	2/23/2006
UT S'western	Tomlinson	PROSE,MAGIC	93	78	8/5/2004
Chicago	Olopade	PROSE,MAGIC	84	69	7/6/2006

Utah/Irvine	Neuhausen	PROSE,MAGIC	364	287	8/8/2006
Women's Coll.	Narod	PROSE,MAGIC	127	70	6/23/2005
Yale	Matloff	PROSE	156	NA	10/10/2006
Total			**4,196**	**2,277**	

*Numbers reflect everyone sent to date for either PROSE and/or Modifiers
**DNA is collected on MAGIC women only.

NEWS

Welcome New Centers: In the past months, we have obtained agreements and begun to receive data from new centers: the Kathleen Cuningham Foundation Consortium for research into Familial Breast cancer (KConFab; http://www.kconfab.org), a multicenter consortium from Australia and New Zealand (Georgia Chenevix-Trench), and The Jonsson Cancer Center at UCLA (Patricia Ganz). We also have begun to work with Guy's Hospital in London to develop them as a PROSE center as well.

New E-mail: Please note the Tara's e-mail address has changed: tfriebel@mail.med.upenn.edu. However, the old address will still work.

The DCIS and BRCA1/2 Cohort Study at Yale University: Elizabeth Claus has initiated a study of DCIS in collaboration with the PROSE/MAGIC consortium. Below is a synopsis of the study, as prepared for potential participants. For questions or to let Elizabeth know about your interest in participating, please contact her at: claus@biomed.med.yale.edu

What is DCIS?
Ductal carcinoma in-situ is a non-invasive form of breast cancer. As recently reported, some patients with DCIS may have genetic mutations in two genes associated with breast and ovarian cancer, BRCA1 and BRCA2.

What is the goal of the study?
Little is known about women with DCIS and who have genetic mutations in BRCA1 or BRCA2. The goal of this project is to form a group (cohort) of such women to better study the prognosis and outcomes for this group of women.

Who is organizing the study?
The study is organized by Dr. Elizabeth B. Claus at the Yale University School of Medicine in collaboration with Dr. Timothy Rebbeck (PI of the PROSE study at the University of Pennsylvania). The study is funded by the Susan G. Komen Breast Cancer Foundation.

The Susan G. Komen Breast Cancer Foundation

Who can enter the study?
Any woman over the age of 20 years who had been diagnosed with DCIS and who has a genetic mutation in either BRCA1 or BRCA2.

What are study participants asked to do?
There are two parts to being a study participant: 1) a telephone questionnaire (30 minutes) with questions on medical and family history, and 2) a mouthwash sample that will allow us to look at changes in DNA. If you allow us, we will also review your tissue specimens and mammograms.

How can an interested person contact the study to get more information?
You may call us (collect) at 203-764-9084 or email the study at stacey.petruzella@yale.edu. You may also visit the websites http://publichealth.yale.edu/news/april06/claus.html or http://www.komen.grants to learn more about the investigators and about the study.

Codebook Update: We have begun a process of revising and updating our codebooks based on comments from the centers and experience in working with the data. We anticipate no major changes, but will incorporate some additional variables and codings. If you have noticed any coding issues that you would like to change, or other suggestions for improvement, please email those to Tara (tfriebel@mail.med.upenn.edu).

Data Collection Focus: In the coming year, we have identified two areas of focus for data collection:

1) *Follow-up Data*: we would like to receive follow up data on all eligible participants.
2) *Tumor markers*: In order to address the hypothesis of our recently funded grant, we are hoping to collect more complete tumor marker data on all breast cancer cases, including ER, PR, and HER2 status.

NCI Consortium

The PROSE/MAGIC group has been designated as an emerging NCI consortium. This allows us to obtain funding for meetings and possibly for research in the future. We are listed on the NCI consortium web site, and will have access to NCI portals for our research: http://epi.grants.cancer.gov/Consortia/table.html#br_ovar

Databse/Website:

- Stephen Gallagher at Penn has been working on building a new database for the study. This is a database built in FilemakerPro. If interested, sites may access their data over a secure web server. Let Tara (tfriebel@mail.med. upenn.edu) know if you would be interested in exploring this option. You would be able to make updates, changes and add new information to your own data over the web.

- The PROSE web site being updated! Information contained on this web site includes contact information, protocols, forms, and research progress.

PROSE Studies Update

RECENT PROSE PUBLICATIONS

One paper was published in the past year by the PROSE group:

- Domchek SM, Friebel TM, Neuhausen SL, Wagner T, Evans G, Isaacs C, Garber JE, Daly MB, Eeles R, Matloff E, Tomlinson GE, Van 't Veer L, Lynch HT, Olopade OI, Weber BL, Rebbeck TR (2006) Mortality Reduction After Risk-Reducing Bilateral Salpingo-Oophorectomy In A Prospective Cohort of *BRCA1* And *BRCA2* Mutation Carriers, *Lancet Oncology,* 7(3):223-9.

In addition, two abstracts were submitted that are currently being prepared or have been submitted for publication:

- Kauff ND, Domchek SM, Friebel TM, Robson ME, Lee J, Garber JE, Isaacs C, Evans G, Lynch HT, Eeles R, Neuhausen S, Daly MB, Matloff E, Blum J, Sabbatini P, Hudis C, Norton L, Barakat RR, Offit K, Rebbeck TR (2007) Risk-Reducing Salpingo-Oophorectomy for the Prevention of *BRCA1* and *BRCA2* Associated Breast and Gynecologic Cancer: A Multi-Center, Prospective Study, *submitted*.
- Friebel TM, Domchek S, Rebbeck TR for the PROSE Study Group (2007) Utilization of Bilateral Prophylactic Oophorectomy and Mastectomy in a prospective series of unaffected BRCA1 and BRCA2 (B1/2) Mutation Carriers. In Preparation.

MAGIC Studies Update

MODIFERS WORK IN PROGRESS

- DNA REPAIR GENES (Work being led by Tim Rebbeck at Penn): As you know, the primary hypotheses of the modifiers of Cancer Risk grant are to evaluate genes involved in DNA damage recognition and repair as modifiers of *BRCA1/2*-associated breast cancer risk. We have generated our candidate gene lists, and simultaneously developing assays for genotyping on all eligible participants. The candidate genes of interest include those that interact with *BRCA1* and/or *BRCA2*, and include: *MRE11, Rad50, NBS1, TopB1, BACH1, CtIP*, and others such as MDM2. At each locus, we have identified haplotype tagged SNPs (htSNPs) as well as candidate functional SNPs. Complete haplotypes are being generated at each of these loci, and associations of these haplotypes with breast and ovarian cancer risk, accounting for other risk factors, are being analyzed.

- IGF PATHWAY GENES (Work being led by Susan Neuhausen at UCI): The goal of this project is to identify variants in genes involved in the insulin-like growth factor (IGF) signaling pathway that modify *BRCA1/2*-associated cancer risk. We have now optimized all the Taqman and SNPLEX assays to genotype the haplotype-tagging SNPs and functional SNPs within the genes and have

completed all the Taqman assays on samples sent last year. We are beginning data analysis this month on the first set of samples.

CIMBA CONSORTIUM

The "Consortium of Investigators of Modifiers of BRCA1/2" (CIMBA) has the goal of finding genetic modifiers of BRCA1/2-associated cancer risks. CIMBA has now met three times, most recently last fall in Lyon, where Tim Rebbeck, Susan Neuhausen, and Fergus Couch represented the MAGIC consortium. Two future meetings of this group are planned:

Copenhagen, May 4-5, 2007
Barcelona, February 1-2, 2008

Georgia Chenevix-Trench at The Queensland Institute of Medical Research in Brisbane has been leading the organization of this effort. Centralized data collection and analysis are being undertaken by Antonis Antoniou at Cambridge. A core set of data elements and common analytical protocol has been identified that must be submitted if a participant is to be included in research studies.

A series of CIMBA research studies has been proposed, including a genome-wide association study and pooled analyses of existing genotype data available for CIMBA members. MAGIC has proposed to lead the CIMBA studies of BRCA-interacting proteins and the IGF pathway, which is consistent with the goals of our R01 grants. We have already contributed data from MAGIC for Rad51 and STK1 and manuscripts are in preparation. Susan Neuhausen's lab is genotyping an additional 4 SNPs for centers that agreed to participate.

Visit us on the Web at: http://www.cceb.upenn.edu/prose/