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

July 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 June 30, 2007 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	22	0	4/15/2002
Baylor-Dallas	Blum	PROSE,MAGIC	21	15	5/23/2006
Beth Israel	Tung	PROSE,MAGIC	86	36	6/29/2007
City of Hope	Weitzel	PROSE,MAGIC	119	119	3/3/2007
Creighton	Lynch	PROSE,MAGIC	290	307	5/2/2007
Dana Farber	Garber	PROSE,MAGIC	330	171	5/10/2007
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	120	71	4/14/2007
kConFab	Trench	PROSE,MAGIC	815	815	10/6/2006
UCLA	Ganz	PROSE,MAGIC	91	85	6/28/2007
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/Rebbeck	PROSE,MAGIC	435	418	9/1/2006
Marsden	Eeles	PROSE	110	NA	5/31/2007
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	97	69	4/10/2007
Utah/Irvine	Neuhausen	PROSE,MAGIC	364	265	8/8/2006
Women's Coll.	Narod	PROSE,MAGIC	127	70	6/23/2005
Yale	Matloff	PROSE	156	NA	10/10/2006
Total			**4,364**	**3,136**	

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

NEWS

New Codebook:

- We have revised our codebook. Please see attached. Please look over the codebook and e-mail Tara with any questions or concerns you may have regarding the codebook. The codebook changes were made based on comments from the centers and experience in working with the data. It incorporates some additional variables and codes. We are in the process of converting the database to reflect the updated version of the codebook, so please if you have changes you want to make or notice any typos. Please tell us now! 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). **Once our codebook is complete a FINAL CODEBOOK will be circulated and we will request that all new data be sent in the new codebook format.**

Data Collection Focus: Areas of focus for data collection:

1) *Follow-up Data*: We would like to receive follow up data on ALL living participants.
2) *Tumor markers*: In order to address the hypothesis of our recently funded grant, we are hoping to collect complete tumor marker data on all breast cancer cases, including ER, PR, and HER2 status. This includes missing tumor marker data on participants already submitted.
3) *Data deadline:* Please have all new and updated data submitted by **September 1, 2007**. Data/DNA submitted after this date will not be included in the next round of analysis.

DATABASE/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 is being updated. Information contained on this web site includes contact information, protocols, forms, and research progress. Please go to: **http://www.cceb.upenn.edu/prose/**

Welcome New Centers: In the past months, we have obtained agreements and begun to receive data and /or DNA from new centers. We have received DNA samples from Dr. Eitan Friedman from Chaim Sheba Medical Center in Israel. Dr. Friedman's center will be participating in both MAGIC and PROSE. New centers working on the IRB stages for PROSE participation include Drs Louise Izatt and Gabriella Pichert from Guy's Hospital in London and Dr. Jeffrey Goldberg from Louisville Oncology in Kentucky.

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

PROSE Studies Update

PROSE PUBLICATIONS AND ABSTRACTS

Two papers are currently being 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, *submitted*.

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, CtlP*, 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 are in the process of completing the genotyping by the end of the summer. We have begun data analysis on the 1689 samples with both DNA and codebook data for SNPs and haplotypes in linkage disequilibrium blocks for IGF1, IGFBP1, IGFBP2, IGFBP5, IGF1R, IRS1, and SHBG. Preliminary analyses showed highly significant associations with breast cancer in both *BRCA1* and *BRCA2* for a SNP in *IGFBP2* and a SNP in LD group 6 of *IGF1R*, and different SNPs in *IGFBP1* and their haplotypes for *BRCA2*.

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 four times, most recently in Copenhagen in early May. Tim Rebbeck, and Fergus Couch represented the MAGIC consortium. The next CIMBA meeting is in 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 under secondary review or published, respectively. Susan Neuhausen's lab genotyped an additional 4 SNPs for centers that agreed to participate and those data are being analyzed. For the next set of SNPs, interested centers can send their DNA samples to Georgia Chenevix-Trench or receive reagents and perform their own genotyping. Details were provided in an e-mail sent by Susan Neuhausen.

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