



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

July 2006 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 July 1, 2006 is provided in the following table. Please contact Tara Friebe Klingner (tklingne@cceb.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 either PROSE or Modifiers, and are interested in participating in the other study as well, please contact us.

Center ID	PI	Study	Data Received *	DNA Received**	Data last updated
Austria	Wagner	Modifiers	296	283	3/29/2006
Baylor-Houston	Plon	Modifiers	21	0	4/15/2002
Baylor-Dallas	Blum	Both	22	14	5/23/2006
Beth Israel	Tung	Both	45	20	7/7/2006
City of Hope	Weitzel	Modifiers	84	119	1/26/2006
Creighton	Lynch	Both	290	233	1/9/2006
Dana Farber	Garber	Both	281	124	2/23/2006
Duke	Schildkraut	Modifiers	41	0	1/1/2002
Evanston N'western	Rubinstein	Both	39	30	2/16/2006
Fox Chase	Daly	Both	114	54	6/7/2006
Georgetown	Isaacs	Both	122	126	4/17/2005
Mayo	Couch/Hartmann	Modifiers	105	104	12/9/2005
NKI	Van 't veer	PROSE	127	NA	11/1/2002
Penn	Domchek/Rebbeck	Both	436	376	5/23/2006
Marsden	Eeles	PROSE	75	NA	5/3/2006
St. Mary's	Evans	PROSE	313	NA	2/23/2006
UT S'western	Tomlinson	Modifiers	93	78	8/5/2004
Chicago	Olopade	Both	84	69	7/20/2005
Utah/Irvine	Neuhausen	Both	322	271	4/27/2006
Women's Coll.	Narod	Both	127	70	6/23/2005
Yale	Matloff	PROSE	149	NA	4/11/2006
Total			3,186	1,971	

*Numbers reflect everyone sent to date for either PROSE and/or Modifiers

**DNA is collected on Modifiers eligible women only.

NEWS

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 will be listed on the NCI consortium web site, and will have access to NCI portals for our research.

PROSE/MAGIC RESEARCH CONFERENCE

In conjunction with the NCI consortium designation, the PROSE/MAGIC group has begun to plan a scientific symposium tentatively titled "Prediction and Prevention of Cancer Risks in *BRCA1/2* Mutation Carriers" in 2007. The meeting will be open to all PROSE/MAGIC consortium members and affiliates, and will be a scientific symposium involving investigators who lead prophylactic surgery and modifiers studies in *BRCA1/2* mutation carriers. More information about the program, attendance, and agenda will follow.

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 Klingner (tklingne@cceb.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 located at: www.cceb.upenn.edu/prose. Information contained on this web site includes contact information, protocols, forms, and research progress. Please be patient with us, as we are going to update the website soon!

PROSE Studies Update

PROSE GRANT COMPETING CONTINUATION:

The PROSE grant (R01-CA102776) funding began this past year, and we have begun to undertake the research outlined in this grant. The Specific Aims of the competing continuation grant are as follows:

- Specific Aim 1: Evaluate the effect of post-BPO HRT use on breast cancer risk reduction.
- Specific Aim 2: Evaluate whether the timing of BPO with respect to age and reproductive events affects the magnitude of cancer risk reduction.
- Specific Aim 3: Evaluate the effect of HRT and BPO on histopathological and biomarker-based characteristics in breast tumors, considering tumors arising from inherited *BRCA1* and *BRCA2* mutations separately.

PROSE PUBLICATIONS AND ABSTRACTS IN 2005-2006

A number of recent papers and abstracts have appeared using PROSE data this past year. Two papers have appeared:

- Rebeck TR, Friebel T, Wagner T, Lynch HT, Garber JE, Daly MB, Isaacs C, Olopade OI, Neuhausen SL, Van 't Veer L, Eeles R, Evans DG, Tomlinson G, Matloff E, Narod SA, The PROSE Study Group, Eisen A, Domchek S, Armstrong K, Weber BL (2005) Effect Of Short Term Hormone Replacement Therapy On Breast Cancer Risk Reduction After Bilateral Prophylactic Oophorectomy In *BRCA1* And *BRCA2* Mutation Carriers. *Journal of Clinical Oncology*, 23(31):7804-10.
- 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, Rebeck 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 to these papers, two abstracts were submitted that will shortly become full papers:

- N. D. Kauff, S. M. Domchek, T. M. Friebel, J. B. Lee, R. Roth, M. E. Robson, R. R. Barakat, L. Norton, K. Offit, T. R. Rebeck, and the PROSE Study Group (2006) Multi-center prospective analysis of risk-reducing salpingo-oophorectomy to prevent *BRCA*-associated breast and ovarian cancer, ASCO Annual Meeting Abstract.
- Friebel TM, Domchek S, Rebeck TR for the PROSE Study Group (2006) Utilization of Bilateral Prophylactic Oophorectomy and Mastectomy in a prospective series of unaffected *BRCA1* and *BRCA2* (B1/2) Mutation Carriers. AACR Meeting Abstract.

MAGIC Studies Update

MODIFIERS WORK IN PROGRESS

- DNA REPAIR GENES (Work being led by Tim Rebeck 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 assays to genotype the haplotype-tagging SNPs and functional SNPs within the genes and are in the process of identifying htSNPs in

an additional set of genes involved in this pathway (including IGF1R, IGF1R, and SHBG, in approximately 1490 samples. We are also plating the samples that we have received in the past couple months. We will begin data analysis shortly on the first set of samples.

CIMBA CONSORTIUM

As many of you are aware, a consortium of investigators from around the world has formed the “Consortium of Investigators of Modifiers of BRCA1/2” (CIMBA) to find genetic modifiers of BRCA1/2-associated cancer risks. The goal of CIMBA is to provide sufficient sample sizes to allow larger scale studies of genetic modifiers. At this point, most groups who have large collections of BRCA1/2 mutation carriers with DNA and risk factor information have become part of the consortium. Representatives of the groups met in Salt Lake City during last year’s ASHG meeting, and again this past spring in Heidelberg (Fergus Couch represented the MAGIC consortium at that meeting).

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 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 that other CIMBA members be included in our research. For the moment, MAGIC can serve as the liaison between the individual centers and CIMBA: As calls for data or research studies are made, we will pass these on to each center PI, who can determine whether they wish to participate. In many cases, individual centers will interact directly with CIMBA to participate in research. If you have questions about your potential participation in CIMBA, please contact Tim Rebbeck by phone at 215-898-1793 or by email at trebbeck@cceb.med.upenn.edu.

Future interactions of MAGIC and CIMBA are ongoing. A number of MAGIC investigators plan to attend the next CIMBA meeting, to be held at IARC in Lyon in October 20-21, 2006. The following CIMBA meeting will take place in Copenhagen Denmark May 2-5, 2007.

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