



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

July 2005 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 Modifiers research studies.

General News

DATA AND BIOSAMPLE COLLECTION

We are on target with our data and biosample accrual goals. Our data collection as of July 1, 2005 is provided in the following table. Please contact Tara Klingner if your center's numbers look incorrect, or if you have additional data 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/DNA last updated
Austria	Wagner	Modifiers	232	232	11/16/2004
Baylor-Houston	Plon	Modifiers	22	8	4/15/2002
Baylor-Dallas	Blum	Both	22	21	1/4/2005
City of Hope	Weitzel	Modifiers	0	84	2/11/2005
Creighton	Lynch	Both	212	146	6/1/2005
Dana Farber	Garber	Both	200	124	6/15/2005
Duke	Schildkraut	Modifiers	41	18	1/1/2002
Fox Chase	Daly	Both	94	10	5/18/2005
Georgetown	Isaacs	Both	105	126	6/9/2005
Mayo	Couch/Hartmann	Modifiers	0	59	5/27/2005
NKI	Van 't veer	PROSE	127	NA	11/1/2002
Penn	Domchek/Rebbeck	Both	313	168	5/15/2005
Marsden	Eeles	PROSE	65	NA	3/5/2005
St. Mary's	Evans	PROSE	189	NA	11/14/2003
UT S'western	Tomlinson	Modifiers	93	78	8/5/2004
Chicago	Olopade	Both	44	69	5/9/2005
Utah/Irvine	Neuhausen	Both	288	223	11/22/2004
Women's Coll.	Narod	Both	127	74	5/2/2005
Yale	Matloff	PROSE	118	NA	4/15/2005
Total			2,292	1,440	

*Numbers reflect everyone sent to date for either PROSE and/or Modifiers (includes 78 ineligible women)

**DNA is collected on Modifiers eligible women only.

WELCOME NEW COLLABORATORS!

We would like to welcome three new sites that have recently joined one or both of our collaborative studies. Our new collaborators include Jeffrey Weitzel from City of Hope, Patricia Ganz from UCLA and Wendy Rubinstein from Northwestern.

ASHG CONFERENCE, SALT LAKE CITY, OCTOBER 24-29, 2005

The PROSE/Modifiers group has not met in person for a couple of years now. Therefore, we would like to hold an ancillary meeting for the PROSE and Modifiers study groups in conjunction with the ASHG meeting in Salt Lake City this fall. We have scheduled this as a dinner meeting on Tuesday October 25, 2005 from 6:30-8:30 pm in Room 151AB of the Utah Convention Center. This meeting will be listed in the meeting program as the "BRCA1/2 Collaborative Centers Meeting: PROSE and Modifiers". Details about the meeting agenda will be sent as the time approaches.

DATABASE/WEBSITE:

- Stephen Gallagher at Penn has been working on building a new database for the study. This is a database built in filemaker pro. If interested, sites may access their data over a secure web server. Let Tara Klingner (tfriebel@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.

PROSE Studies Update

PROSE GRANT COMPETING CONTINUATION:

The PROSE grant (R01-CA102776) will be refunded! We have not heard when the continued funding will begin, but this will ensure our continued collection and follow-up of the valuable cohort we have assembled. 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.

The abstract and grant text will be posted on the PROSE web site for your information.

PROSE PUBLICATIONS

- “Effect of Short Term Hormone Replacement Therapy On Breast Cancer Risk Reduction after Bilateral Prophylactic Oophorectomy In *BRCA1* and *BRCA2* Mutation Carriers” was accepted by JCO. The abstract of this paper is as follows:
Background: Bilateral prophylactic oophorectomy (BPO) is widely used for cancer risk reduction in women with *BRCA1/2* mutations. Many premenopausal women choose to take hormone replacement therapy (HRT) after undergoing BPO to abrogate immediate symptoms of surgically-induced menopause. Thus, we evaluated whether the breast cancer risk reduction conferred by BPO in *BRCA1/2* mutation carriers is altered by use of post-BPO HRT. *Methods:* We identified a prospective cohort of 462 women with disease-associated germline *BRCA1/2* mutations at twelve medical centers to evaluate breast cancer risk after BPO with and without HRT. We determined the incidence of breast cancer in 155 women who had undergone BPO and in 307 women who had not undergone BPO in whom we had complete information on HRT use. Post-operative follow-up was 3.6 years. *Results:* Consistent with previous reports, BPO was significantly associated with breast cancer risk reduction overall (HR=0.40, 95%CI: 0.18-0.92). Using mutation carriers without BPO or HRT as the referent group, HRT of any type after BPO did not significantly alter the reduction in breast cancer risk associated with BPO (HR=0.37, 95% CI: 0.14-0.96). *Conclusions:* Short term HRT use does not negate the protective effect of BPO on subsequent breast cancer risk in *BRCA1/2* mutation carriers.
- “Reduction in short-term mortality after bilateral prophylactic oophorectomy in *BRCA1* and *BRCA2* mutation carriers” is being circulated for comment. The abstract of this work is as follows:
Background: Bilateral prophylactic oophorectomy (BPO) is widely used for cancer risk reduction in women with *BRCA1/2* mutations. BPO reduces risk of subsequent breast and ovarian cancers, but the reduction in mortality following this surgery is not well understood. We evaluated whether an improvement in overall or cancer-specific mortality was conferred by BPO in *BRCA1/2* mutation carriers. *Methods:* A prospective cohort of 431 women with disease-associated germline *BRCA1/2* mutations at fourteen medical centers was identified to evaluate breast cancer risk after BPO. Overall and cancer-specific mortality were determined in 151 women who had undergone BPO and 280 matched women who had not undergone BPO. Mean post-BPO follow-up was 2.4 years. *Results:* Among women who underwent BPO, overall mortality was reduced by 71% (hazard ratio (HR) =0.29, 95% CI: 0.10-0.81), breast cancer-specific mortality was reduced by 86% (HR=0.14, 95% CI: 0.03-0.80), and ovarian cancer-specific mortality was reduced by 87% (HR=0.13, 95% CI: 0.05-0.35). *Conclusions:* Overall and cancer-specific mortality is substantially reduced in women with *BRCA1/2* mutations who have undergone BPO.
- ER/PR: Susan Domcheck at Penn is exploring the ER/PR status of breast tumors in women who have and have not undergone BPO. To accommodate this research, a new section has been added to the codebook that collects additional medical records data related to ER/PR. Please note these changes in the codebook and provide these data with your ongoing data submissions.

MODIFIERS Studies Update

MODIFIERS PUBLICATIONS

- AIB1/SMOKING: Using pre-existing data, Susan Colilla at Penn has drafted a manuscript entitled “Modification of breast cancer risk by smoking and AIB1/NCOA3/SRC3 genotype in women who have inherited a *BRCA1* mutation”. This manuscript has been resubmitted and we will notify you when the decision about publication is made.
- RAD51: Using data generated by Susan Neuhausen at UCI, we are undertaking analyses evaluating genotypes of *RAD51* and breast cancer risk in *BRCA1/2* mutation carriers. As soon as the analyses are complete and a manuscript is drafted, it will be sent along to you for comment.

MODIFIERS WORK IN PROGRESS

- DNA REPAIR GENES (Work being led by Tim Rebbeck and Kate Nathanson 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.
- 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. We are genotyping the samples we have received and have genotyped the SNPs in *IGF1R*, *SHBG*, *IGF1*, and two SNPs in *IRS1*. We have not begun data analysis as there are too few samples for sufficient power.
- It is a major goal of both studies to have genotype data by the summer of 2005. Thus, we hope to receive from each center as many DNA samples as possible by mid-Summer 2005 so that we can efficiently perform the laboratory studies. For those that have already sent their first batch of samples, there may be additional carriers now identified.