



Modifiers of Cancer Risk in BRCA1/2 Mutation Carriers

January 2005 Newsletter

HAPPY NEW YEAR!

We would like to introduce the first in a quarterly series of newsletters that we will use to provide you with updates on current events.

As you know, the Modifiers grant was funded July 1, 2004!! Since then we have begun collecting data and DNA samples, and anticipate many interesting upcoming analyses.

DATA ACRRUAL:

MODIFIERS Data and DNA Collection Summary as of 1/5/2005

Center ID	No. Currently in Database	No. of DNA samples sent	No. Eligible w/DNA*	Data/DNA last updated/sent
AU	232	232	223	11/16/2004
BU	22	0	?	NA (data abstracted from old Modifier database)
CH	0	0	74	
CR	0	10	289	12/2/03
DF	0	0	231	
DU	41	0	?	NA (data abstracted from old Modifier database)
FC	35	10	46	1/5/2005
GU	0	54	183	12/17/2004
UP	202	202	207	12/22/2004
SW	93	78	109	8/5/2004
UT/UCI	0	223	255	11/22/2004
WC	0	74	82	10/14/2004
MC	0	0	?	
COH	0	0	127	1/4/2005
Total	620	681	1826*	

*Current expected sample size once current data submissions are completed.

DATABASE

Steven Gallagher at Penn has been working on building a new database for the study. This is a database built in filemaker pro. It is able to link the data and the DNA directly with the lab, using the "universal ID" (UID) generated for all participants in this study. If interested, sites may access their data over a secure web server. Let Tara Friebe (tfriebe@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.

To note: If your site participates in both the PROSE study and the Modifiers study (collectively referred to as the Carrier Study), you will receive two newsletters, with some overlapping information. In addition, the content of the databases also overlaps substantially.

CURRENT MANUSCRIPTS:

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". The abstract of this manuscript is as follows:

Women with *BRCA1* mutations are at an elevated risk for breast cancer, and AIB1 (NCOA3/SRC3) genotype may alter this risk. We examined the differences in breast cancer risk by AIB1 poly-glutamine repeat polymorphism and pre-diagnosis smoking habits for *BRCA1/2* mutation carriers to determine if there was an interaction between smoking and AIB1 genotype. In 363 female *BRCA1* mutation carriers, multivariate Cox proportional hazard regression was used to model breast cancer risk. Ever having smoked was associated with a decreased breast cancer risk (Hazard Ratio (HR): 0.72, 95% CI: 0.53, 0.97). A dose-response relationship between number of pack-years smoked and breast cancer risk was also found for women who smoked < 20 pack years of cigarettes (HR: 0.82, 95%CI: 0.79, 1.00) and for women who smoked = 20 pack years (HR: 0.46, 95%CI 0.26, 0.79; p for trend = 0.005). Women with a 28 repeat allele for AIB1 had a significantly reduced risk of breast cancer (HR=0.68, 95% CI: 0.49, 0.96). Women who smoked =20 pack-years with a 28 repeat allele had an even greater reduced risk of breast cancer (HR=0.10, 95% CI: 0.02, 0.50) compared to women who were never smokers with no 28 allele.

Since AIB1 appears to modulate the effect of endogenous hormones via the estrogen receptor, and smoking is considered to affect circulating hormone levels, these results support evidence that steroid hormones play an important role in breast carcinogenesis in BRCA1 mutation carriers, and suggest mechanisms for developing novel cancer prevention strategies for BRCA1 mutation carriers.

RAD51: Using data generated by Susan Neuhausen at UCI, we are completing 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.

RESEARCH IN PROGRESS:

ER/PR: Susan Domcheck at Penn is exploring the ER/PR status of breast tumors. 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.

DNA REPAIR GENES: As you know, the primary hypotheses of this grant are to evaluate genes involved in DNA damage recognition and repair as modifiers of BRCA1/2-associated breast cancer risk. Tim Rebbeck and Kate Nathanson at Penn are generating our candidate gene lists, and simultaneously developing assays for genotyping on all eligible participants. It is a major goal of this study to have genotype data by the summer of 2005. Thus, we hope to receive from each center as many DNA samples as possible by early Spring so that we can efficiently begin the laboratory studies.