Author’s response to reviews

Title: The Prevalence of BRCA Mutations Among Young Women with Triple-Negative Breast Cancer

Authors:

S R Young (sryoung37@aol.com)
Robert T Pilarski (robert.pilarski@osumc.edu)
Talia Donenberg (tdonenberg@med.miami.edu)
Charles Shapiro (charles.shapiro@osumc.edu)
Lyn S Hammond (hammondl@musc.edu)
Judtih Miller (Miller12@uiuc.edu)
Karen A Brooks (Kabrooks@richmed.medpark.sc.edu)
Stephanie Cohen (sacohen@stvincent.org)
Beverly Tenenholz (btenenholz@geisinger.edu)
Damini DeSai (ddesai@covhs.org)
Inuk Zandvakili (inukzand@gmail.com)
Robert Royer (robert.royer@wchospital.ca)
Song Li (song.li@wchospital.ca)
Steven A. Narod (steven.narod@wchospital.ca)

Version: 3 Date: 21 October 2008

Author’s response to reviews:

October 18, 2008

Dr Scott Edmunds,

Senior Editor,

BMC Journals

MS: 9481053432061545 - The Prevalence of BRCA Mutations Among Young Women with Triple-Negative Breast Cancer

Dear Dr. Edmunds

Thank you for considering publishing our manuscript in BMC Cancer. We have revised the manuscript having taken into consideration the reviewers comments. I would like to respond to the reviewers comments in turn:

Reviewer 1. Tommiska

We have changed the title and abstract to reflect the concern of the reviewer.
The study was principally focused on BRCA1. (We screened the two large exons of BRCA2 with PTT because this was an inexpensive addition – funds were not available to complete the sequencing of BRCA2).

The reviewer notes correctly that all tumours were high-grade. To my knowledge no triple-negative tumours were excluded from the study based on grade and over 90% of triple negative tumours are of high-grade. We have corrected the text throughout to indicate that the tumours were high grade.

We have divided table 1 into two tables and have added age-of-onset and ethnic group.

Reviewer 2. Sng

We have clarified the ages of onset of the cancers with mutations in table 1.

We have changed the title to better reflect the content of the paper.

The references have been corrected.

Reviewer 3. Chang

Dr Chang discusses the issue of whether or not a family structure is predictive of a mutation in a triple-negative patient with a negative family history. She poses the question: if a young woman has a negative family history, can she be excluded as a candidate for genetic testing based on a high number of unaffected female relatives?

I do not support this position for the following reasons: The key article in question is that by Weitzel and colleagues, was published in JAMA in 2007. Limited family structure and BRCA gene mutation status in single cases of breast cancer. This was a poor article and was misleading for the following reasons:

They describe the patient population as eligible if they were under 50 and had a negative family history. Nevertheless, their study population was far from a random sample of women under 50 with breast cancer. The average age of the included patients was 37. Furthermore the majority of mutations found in the population were founder mutations in the Jewish and Hispanic populations – there is a clear case for testing all Jewish and Hispanic patients for the founder mutations – and it is not necessary to take family history into account. This is why we excluded Jews from our study. The overall prevalence of mutations in the Weitzel paper for supposedly ‘unselected’ breast cancer patients with no family history under age 50 was 9.5%. This is impossibly high and reflects the highly-selected nature of his population. In contrast the prevalence of mutations in our study of high-grade triple-negative patients under age 40 was 11%. I believe our estimate to be accurate and prefer not to cite the Weitzel paper
because it is misleading.

Furthermore, it is not possible for the physician or genetic counselor to use BRCAPRO or BOADICEA at present to predict the presence of a mutation for women with triple-negative cancers because the models do not take triple-negative status into account. I am comfortable with the straightforward recommendation that all women with early onset triple negative breast cancers be tested for BRCA1 mutations. I hope that in the future the predictive models will integrate this.

Reviewer 4. Roukos

We agree with the reviewer and have changed the abstract as requested

We enclosed the revised manuscript and hope that it is satisfactory

Yours truly,

Steven Narod