Genetics of Cognitive Decline Post Cancer Chemotherapy: DNA Repair Genes

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Introduction

Adjuvant chemotherapy for the treatment of breast cancer has been associated with cognitive decline in a subgroup of survivors, suggesting that genetic factors may increase risk for post-treatment cognitive changes. DNA damage has been proposed as a mechanism of chemotherapy-induced cognitive change because of the impact of chemotherapy on DNA and the association of DNA damage with cognitive changes associated with normal aging and increased risk for neurodegenerative diseases. Therefore, the goal of this study was to examine the association of post-treatment cognitive changes and DNA repair genes in breast cancer patients.

Methods

Breast cancer patients were evaluated with a battery of neuropsychological tests prior to chemotherapy and at 1, 6, and 18 months post-chemotherapy (N=69, age=52.7+/-8.2, education=15.5+/-2.6). Matched groups of breast cancer patients not exposed to chemotherapy (N=79, age=57.5+/-9.8, education=14.8+/-2.3) and healthy controls (N=57, age=53.3+/-9.8, education=15.2+/-2.1) were evaluated at similar intervals. Genotyping was done with an Affymetrix chip which was designed by the investigators to assess candidate SNPs in the following pathways including DNA repair genes.

Forty-two SNPs from the DNA repair pathway were initially identified. SNPs were removed from the analysis if there were less than 5 participants in a group for a given allele; consequently, 17 SNPs were entered into the analysis. In order to maximize sample size, a series of linear regression analyses were conducted with cancer patients vs. control by allele as the grouping variable, age and education, and drinking history (all associated with change in Processing Speed) as covariates and change from baseline scores in Processing Speed as the primary outcome measure. The same analysis was repeated with chemotherapy, no chemotherapy, and controls as the grouping variable. To control for multiple comparisons, p values were adjusted utilizing FDR analyses.

Results

The analysis of patients vs. controls identified two SNPs from the meiotic recombination 11 homolog A (MRE11A) gene (rs 472344 and rs 535801). The

strongest effect was seen at the 18 month assessment where patients who were homozygous for the minor allele performed significantly worse on Processing Speed compared to patients with other forms of the allele (rs 472344, $p=0.0074$, FDR $p<0.1$ and rs 53580, $p=0.00048$, FDR $p<0.05$). The analysis that compared chemotherapy, no chemotherapy and healthy control groups suggests that patients who were homozygous for the minor alleles of these SNPs and exposed to chemotherapy had the lowest Processing Speed scores as compared to other forms of the allele (rs 472344, $p=0.047$ and rs 53580, $p=0.016$), although the p-values were not below the FDR cut-off.

Discussion

Understanding genetic factors that increase risk for cognitive changes associated with cancer treatments may lead to an understanding of the molecular mechanisms of cognitive changes in breast cancer survivors and to the development of targeted treatments to prevent or reduce the negative impact of these cognitive changes.