Increased risk of HER2-positive breast cancer among germline CHEK2 mutation carriers with breast cancer.

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Abstract Text:

Background: Checkpoint Kinase 2 (CHEK2) germline mutations have been linked to hereditary cancers, particularly breast cancer, with data suggesting a lower risk of cancer susceptibility for the I157T CHEK2 mutation. There are no data regarding the subtypes of breast cancer including HER2 expression/gene amplification in breast tumors associated with germline CHEK2 mutations.

Methods: We retrospectively reviewed genetic testing records performed in a single laboratory (Ambry Genetics) of women with a history of breast cancer referred for multi-gene panel testing between March 2012 and December 2014. Demographic features analyzed included age and race/ethnicity. Pathological characteristic of HER2 status according to descriptive diagnosis by the ordering physician was compared in women with germline CHEK2 mutation (gCHEK2-m) vs. other germline mutations (gOTHER-m). Cases with multiple germline mutations were excluded. The gCHEK2-m cases included p.I157T moderate risk mutation, the c.1100delC founder mutation, and other *CHEK2*mutations. Fisher's exact test and odds ratio (OR) were utilized to ascertain for any significant difference between gCHEK2-m and gOTHER-m cases.

Results: A total of 6,046 cases were included in the analysis. Mean age at testing was 53 years. Regarding race/ethnicity, the majority of cases were Caucasian (70.1%) followed by African American (5.9%) and Ashkenazi Jewish (5.5%). The gOTHER-m mutations were 66% in *BRCA1*, *BRCA2*, *PALB2*, *TP53*, *PTEN*, and *ATM*, and 34% in other low-moderate risk genes. HER2 positivity was seen more frequently in gCHEK2-m (n = 158) than gOTHER-m (n = 420) (OR, 1.52; 95% CI, 0.95-2.43, p = 0.07). When gCHEK2-m was refined to exclude those with the lower risk of cancer susceptibility I157T CHEK2 mutation (n = 127), compared to gOTHER-m, there was a significant increase in likelihood of HER2 positive breast cancer (OR, 1.69; 95% CI, 1.02-2.77, p = 0.03).

Conclusions: Our results suggest a possible association between germline CHEK2 mutation and HER2 positive breast cancer. If confirmed in larger data sets, these results could prompt further investigation in the molecular pathway linking CHEK2 and HER2 overexpression/amplification in breast cancer.