Revisiting the role of *CHEK2* mutations in hereditary breast-colorectal cancer probands

Kimberly Childers[1], Rachel McFarland[2], Holly LaDuca[2], Ora K Gordon[1]

[1]Providence Health and Services Southern California; [2]Ambry Genetics

kimberly.childers@providence.org

Background: Germline mutations that predispose to both breast and colorectal cancer risk are currently not well defined. A specific mutation in *CHEK2* – p.I157T – has been associated with moderately increased risks for both malignancies, but data is limited. We investigated the prevalence of pathogenic mutations and likely pathogenic variants ("mutations") in *CHEK2*, comparing mutation occurrence in individuals with a diagnosis of breast cancer alone, to those with both breast and colorectal cancer primaries.

Methods: Clinical histories and test results were reviewed for patients undergoing *CHEK2* sequencing and deletion/duplication analysis as part of multi-gene panel testing at one clinical laboratory between April 2012 and June 2015. The study population was limited to women with breast cancer only (n=17,553) and women with both breast and colorectal cancer (n=348) without other primaries. Demographic and clinical information was provided by clinicians on test requisition forms, pedigrees and clinic notes, as available. *CHEK2* mutation frequencies were compared between women with breast cancer only and women with both breast and colorectal cancers using Fisher's exact test.

Results: *CHEK2* p.I157T was significantly more likely to be identified in women with breast and colorectal cancer compared to breast cancer alone. There was no significant difference in the frequency *CHEK2* mutations outside of this locus (1100delC and others) between the two groups (Table 1). Of the 10 women with both breast and colorectal cancers harboring *CHEK2* mutations, the median age at diagnoses of both cancers was over age 50 (51 for breast, 51.5 for colorectal).

Table 1. Mutation Frequencies

Mutation	Mutation Frequency n/N (%)		p	OR [95% CI]
	Breast & Colorectal	Breast Only		
CHEK2 p.I157T	7/348 (2.01%)	106/17,553 (0.60%)	**0.0066**	**3.38 [1.32, 7.28]**
CHEK2 Other	3/348 (0.86%)	363/17,553 (2.07%)	0.13	0.41 [0.08, 1.22]
CHEK2 Total	10/348 (2.87%)	469/17,553 (2.67%)	0.74	1.08 [0.51, 2.02]

Bold text = significant difference

Conclusions: This exploratory study substantiates the previously reported association of the specific missense p.I157T *CHEK2* mutation with predisposition to both breast and colorectal cancer. These findings suggest that this may be a unique feature of p.I157T as compared to mutations in *CHEK2* outside of this locus, such as the common 1100delC mutation, but larger cohorts are needed to investigate whether this locus specific effect in *CHEK2* is maintained. Given the frequency of p.I157T mutations in individuals with dual breast and colorectal primaries, enhanced colorectal cancer screening may be warranted for *CHEK2* p.I157T mutation carriers specifically.