# Increased risk of HER2-positive breast cancer among germline *CHEK2* mutation carriers

Chethan Ramamurthy[1], Raji Shameem[1], Andrea D. Forman[1], Rachel McFarland[2], Jill S. Dolinsky[2], Virginia Speare[2], Carin Espenschied[2], Wafik El-Deiry[1], Michael J. Hall[1], Mary B. Daly[1], Lori J. Goldstein[1], Elias Obeid[1]

Fox Chase Cancer Center, Philadelphia, PA[1]; Ambry Genetics, Aliso Viejo, CA[2]

## Background

- Checkpoint Kinase 2 (*CHEK2*) germline mutations have been linked to hereditary cancers, particularly breast cancer.
- The most widely studied *CHEK2* mutations are the c.1100delC and p.I157T mutations. The p.I157T mutation confers a lower risk of breast cancer than other *CHEK2* mutations.[1-2]
- Germline mutations in *BRCA1/2* have been associated with triple negative breast cancers , and germline *TP53* mutations with HER2 positive breast cancers.[3]
- There are limited data regarding the subtypes of breast cancer including HER2 expression/gene amplification in breast cancers associated with germline *CHEK2* mutations.[4-5]

## Methods

- We reviewed retrospectively collected 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. We included only patients in whom HER2 status was known.
- Demographic features were analyzed, and those included age and race/ethnicity (Table 1, Table 2).
- Pathological characteristics of HER2 status according to descriptive diagnosis by the ordering physician were compared in women with germline *CHEK2* mutation (gCHEK2-m) vs. other germline mutations (gOTHER-m) (Table 4).
- 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 (Table 3).
- Fisher's exact test and odds ratio (OR) were utilized to ascertain for any significant difference between gCHEK2-m and gOTHER-m cases.

## Results

**Table 1 Patient Demographics**

| Ethnicity | Number | Percentage |
|---|---|---|
| African American/Black | 356 | 5.9% |
| Alaskan Native | 1 | 0.0% |
| Ashkenazi Jewish | 335 | 5.5% |
| Asian | 191 | 3.2% |
| Caucasian | 4238 | 70.1% |
| Hispanic | 239 | 4.0% |
| Middle Eastern | 39 | 0.6% |
| Native American | 5 | 0.1% |
| Mixed Ethnicity | 255 | 4.2% |
| Other | 16 | 0.3% |
| Unknown | 371 | 6.1% |

**Table 2 Other characteristics**

| | |
|---|---|
| **Median Age at Testing** | 52 (range: 20-92) |
| **Median Age at Diagnosis of First Breast Cancer** | 48 (range 12-91) |

**Table 3 Definitions of subgroups**

| | |
|---|---|
| **gCHEK2-m (n=158)** | Any *CHEK2* mutation. 1100delC and I157T (N=55) and 24 other unique *CHEK2* mutations (N=103). |
| **gOTHER-m (n=420)** | Any other significant germline mutation. *BRCA1/2* (N=277) *PALB2*, *TP53*, *PTEN*, and *ATM*, and moderate risk genes (N=143) |

**Table 4 HER2 expression among different germline mutation carriers***

| | All Patients | No Mutation | *CHEK2* (Any) | *CHEK2* (without I157T) | *CHEK2* 1100delC | *CHEK2* I157T | *CHEK2* (Other) | Any Non-*CHEK2* (Excluding Multiple Muts) | *BRCA1* | *BRCA2* | *PALB2* | *TP53* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HER2 Positive** | 1274 | 1136 | 38 | 33 | 18 | 5 | 15 | 72 | 6 | 7 | 6 | 7 |
| **HER2 Negative** | 4772 | 4202 | 120 | 94 | 54 | 26 | 40 | 348 | 61 | 45 | 58 | 11 |

* Only patients in whom HER2 status was known were included

**Table 5 Odds ratios for HER2 positivity between different groups**

| | *CHEK2* (Any) | *CHEK2* (without I157T) | *CHEK2* 1100delC | *CHEK2* I157T | *CHEK2* (Other) | Any Non-*CHEK2* | *BRCA1* | *BRCA2* | TP53 |
|---|---|---|---|---|---|---|---|---|---|
| **All Patients** | 0.84 | 0.76 | 0.80 | 1.39 | 0.71 | 1.29 | 2.71* | 1.72 | 0.42 |
| **Negative, Inconclusive** | 0.85 | 0.77 | 0.81 | 1.41 | 0.72 | 1.31* | 2.75* | 1.74 | 0.42 |
| **Any Mutation/VLP** | 0.76 | 0.69 | 0.72 | 1.25 | 0.64 | 1.16 | 2.45* | 1.55 | 0.38 |
| ***CHEK2* (Any)** | | 0.90 | 0.95 | 1.64 | 0.85 | 1.53 | 3.21* | 2.03 | 0.50 |
| ***CHEK2* (without I157T)** | | | 1.05 | 1.82 | 0.94 | 1.69* | 3.55* | 2.25 | 0.55 |
| ***CHEK2* 1100delC** | | | | 1.72 | 0.89 | 1.61 | **3.36*** | 2.13 | 0.53 |
| ***CHEK2* I157T** | | | | | 0.52 | 0.93 | 1.94 | 1.23 | 0.31 |
| ***CHEK2* (Other)** | | | | | | 1.81 | 3.77* | 2.39 | 0.59 |
| **Any Non-*CHEK2*** | | | | | | | 2.10 | 1.33 | **0.33*** |
| ***BRCA1*** | | | | | | | | 0.63 | **0.16*** |
| ***BRCA2*** | | | | | | | | | **0.25*** |

* indicates $p < 0.05$

## Highlighted Findings

- 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).
- We further refined gCHEK2-m to exclude those with the lower risk of cancer susceptibility p.I157T *CHEK2* mutation (n=127). When this group was 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) (Table 5).

## Conclusions

- Our results suggest a possible association between a germline *CHEK2* mutation and a higher risk for HER2 positive breast cancer.
- *BRCA1/2* positive cases are enriched for HER2 negativity ("triple negatives"); therefore a comparison of gCHEK2-m to gOTHER-m may result in an overestimate of the association between a germline mutation in *CHEK2* and HER2 positivity.
- If confirmed in larger data sets, these results could prompt further investigation into the molecular pathway linking *CHEK2* and HER2 overexpression/amplification in breast cancer.

## References

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Please direct questions to Chethan Ramamurthy, MD at chethan.ramamurthy@tuhs.temple.edu