Robson, Mark

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Comprehensive breast cancer (BC) risk assessment for CHEK2 carriers incorporating a polygenic risk score (PRS) and the Tyrer-Cuzick (TC) model

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Germline Pathogenic Variants (PV) in CHEK2 are Common and Lead to a Moderately Increased Risk for Female Breast Cancer

- Lifetime breast cancer risk estimates range from 23% to 48%

- Close to 1% of individuals tested with a hereditary cancer panel carry a CHEK2 PV, 65% of which are 1100del, a European founder PV

- Consistent with the >20% estimated lifetime breast cancer risk, current NCCN guidelines for management of CHEK2 PV carriers include consideration of annual breast MRI screening beginning at age 40
Breast Cancer Risks for CHEK2 Carriers are Modified by Other Factors

• Previous studies have shown that breast cancer risk in women with PV in hereditary breast cancer risk genes, including CHEK2, is modified by:
  • Family history
  • Clinical factors related to lifetime estrogen exposure
  • Multiple low penetrance breast cancer risk variants (SNPs), which we have integrated into an 86-SNP Polygenic Risk Score (PRS)

Goal: Development of a comprehensive risk prediction model for women with CHEK2 PV to more precisely estimate risk incorporating the 86-SNP PRS and the Tyrer-Cuzick model.
Specific Aims

• Expand the Tyrer-Cuzick model (v7) to incorporate CHEK2 risks

• Incorporate PRS into the CHEK2/Tyrer-Cuzick model

• Evaluate risk stratification in CHEK2 PV carriers who were not included in risk model development
Methods: CHEK2 + Tyrer-Cuzick Model Development

Study population: 355,429 women of European ancestry referred for hereditary cancer testing

Exclusions
• Homozygous/compound het
• DCIS, LCIS, or hyperplasia without subsequent BC diagnosis

<table>
<thead>
<tr>
<th></th>
<th>CHEK2 PV Carriers*</th>
<th>Non-Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients</td>
<td>4,286</td>
<td>351,143</td>
</tr>
<tr>
<td>Age Range</td>
<td>18-83</td>
<td>18-84</td>
</tr>
<tr>
<td>Median Age</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>Diagnosed with BC</td>
<td>1,583 (37%)</td>
<td>83,257 (24%)</td>
</tr>
<tr>
<td>≥ 1 FDR with BC</td>
<td>1,856 (43%)</td>
<td>123,915 (35%)</td>
</tr>
</tbody>
</table>

* CHEK2 variants I157T and S428 are not considered PV in this analysis
Methods: CHEK2 + Tyrer-Cuzick Model Development

Considerations for combining CHEK2 with Tyrer-Cuzick:

CHEK2 Risk
- Is 1100delC equivalent to other PVs?
- Is CHEK2 risk age dependent?

Confounding:
- Are Tyrer-Cuzick factors correlated with CHEK2 status? (e.g., BC family history)

Important to prevent double counting of risk

Interaction:
- Do factors in Tyrer-Cuzick confer the same risk to CHEK2 carriers as non-carriers?

Validity of Tyrer-Cuzick for CHEK2 carriers
1100delC was equivalent to other CHEK2 PVs in terms of breast cancer risk.

Odds ratios derived from multivariable logistic regression models predicting breast cancer based on CHEK2 PV status and adjusted for age, Ashkenazi ancestry, personal and familial cancer history.
Methods: CHEK2 + Tyrer-Cuzick Model Development

- CHEK2 risks were consistent with prior literature
- Modest age dependence reported in prior literature for 1100delC was not reproduced

Schmidt et al., 2016

\[ N = 930 \text{ CHEK2 1100delC} \]
\[ N = 70,953 \text{ non-carriers} \]

This study

\[ N = 2,407 \text{ CHEK2 1100delC} \]
\[ N = 351,143 \text{ non-carriers} \]
Methods: CHEK2 + Tyrer-Cuzick Model Development

CHEK2 was combined with the Tyrer-Cuzick model according to a Fixed-Stratified (FS) method\(^1\) that prevents double-counting of information from correlated risk factors in a manner equivalent to full multivariable co-estimation. Briefly,

- Any risk factor showing correlation with CHEK2 status, e.g., family history (FH), was modelled as a predictor of breast cancer (BC) in logistic regression
  
  \[
  \text{Model 1: } BC \sim \beta_1 \times FH
  \]

- The association of CHEK2 with BC was estimated from a model with the effect of FH fixed
  
  \[
  \text{Model 2: } BC \sim \text{offset}(\beta_1 \times FH) + \beta_2 \times \text{CHEK2}
  \]

- Unaffected women (carriers and non-carriers) were stratified according to FH severity

- Absolute remaining lifetime risk for a woman in FH strata \(k\) at \(t\) years of age is
  
  \[
  1 - [1 - \text{Tyrer-Cuzick}(t)]^{\exp(\beta_2 \times \text{CHEK2} + C_k)}
  \]

  where \(C_k\) was calculated to preserve the average Tyrer-Cuzick risk within strata \(k\) after incorporating CHEK2

\[
C_k = -\ln(E[\exp(\beta_2 \times \text{CHEK2})]), \text{ with expected value taken across strata } k
\]

1. Hughes et al., Basser Symposium 2019
Methods: *CHEK2* + Tyrer-Cuzick Model Development

- *CHEK2* status was strongly associated with family history of BC (p-value <10^{-14}).

  Combined according to the Fixed-Stratified method to avoid double counting

- No other Tyrer-Cuzick risk factors showed evidence of association.

- No Tyrer-Cuzick risk factors showed evidence of interaction with *CHEK2* status

  Factors confer the same risk to *CHEK2* carriers as non-carriers
Results: Risk Stratification

Lifetime risk distribution in 459 women with CHEK2 mutations

- Independent cohort
  - Tyrer-Cuzick
  - CHEK2 + Tyrer-Cuzick

Remaining Lifetime Risk

Count
Methods: Incorporate PRS

PRS stratification for *CHEK2* carriers is comparable to non-carriers

This forest plot displays the standardized OR for the association between PRS and personal BC history along with 95% CI for carriers of each gene and non-carriers. * denotes a significant difference (p < 1 x 10^-4) between non-carriers and individuals with a PV in *BRCA1/BRCA2*. # denotes a significant difference (p < .01) between individuals with *CHEK2* mutations and those with a PV in *BRCA1/2*.
**Methods: Incorporate PRS**

- PRS is associated with family history of breast cancer, but not with any other Tyrer-Cuzick risk factors.

  Combined with multivariable adjustment to avoid double counting of risk information

- No Tyrer-Cuzick risk factors showed evidence of interaction with PRS after multiple testing correction (marginal interaction with family history).

  Factors confer essentially the same risk to women with high PRS as low PRS
Results: Risk Stratification

Risk Based on PRS + CHEK2 + Tyrer-Cuzick

- 293 (64%) had risk estimates of 20%-50%
- 111 (24%) had risk estimates ≤ 20%
- 55 (12%) had risk estimates >50%
Results: Risk Stratification

- Risk stratification was increased by incorporating PRS into the model based on CHEK2 + Tyrer-Cuzick.
- Risk estimates can increase or decrease significantly due to PRS.
Limitations

• Analyses were based on data from women referred for hereditary cancer testing; clinical information from test request forms may have been incomplete or inaccurate.

• Further studies are necessary to characterize polygenic breast cancer risk for women of non-European ancestry.

• Additional work is needed to incorporate other important risk factors such as breast density.
Conclusions

- Personalized risk prediction is important for CHEK2 PV carriers because these patients have a wide spectrum of risk that is influenced by many factors.

- Comprehensive risk assessment could improve stratification and inform individualized decision-making for screening and prevention strategies.