Development of a breast cancer risk assessment model for ATM mutation carriers incorporating Tyrer-Cuzick and a polygenic risk score

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BACKGROUND

- Germline pathogenic variants (PVs) in the moderate-penetrance ATM gene confer a ~2-fold increased risk for breast cancer (BC).
- Currently, women with ATM PVs meet the >20% lifetime risk threshold for consideration of enhanced screening recommendations, including screening at younger ages and consideration of breast MRI.
- BC risks for women with inherited PVs in many hereditary breast cancer genes can be adjusted using polygenic risk score (PRS) data, BC family history, and other clinical information.1,2,3

METHODS

- De-identified data from 353,809 women of European ancestry who were tested clinically for hereditary cancer risk with a multi-gene panel were analyzed.
- Model development included ATM PV carriers (N=2,666) and women negative for BC gene PVs (N=351,143) tested between September, 2013 and November, 2019 (carriers) or July, 2019 (non-carriers).
- Women with the high-risk ATM c.7271T>G allele were excluded.

ANALYSIS

- Risk estimates incorporating ATM, PRS, and Tyrer-Cuzick were calculated using a fixed-stratified method that accounted for correlations between risk factors in a manner equivalent to multivariable co-estimation.
- Risk stratification was assessed in an independent cohort of ATM carriers (N=216) who were tested after November, 2019.

RESULTS

Table 1. Patient Demographics

<table>
<thead>
<tr>
<th>ATM PV Carriers</th>
<th>Non-Carriers</th>
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<tbody>
<tr>
<td>Total Patients</td>
<td>2,666</td>
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<tr>
<td>Age Range</td>
<td>18-84</td>
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<tr>
<td>Median Age</td>
<td>49</td>
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<tr>
<td>Diagnosed with BC</td>
<td>916 (34%)</td>
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<tr>
<td>≥ 1 FDR with BC</td>
<td>1,151 (43%)</td>
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- BC risk for ATM PV carriers was approximately double that of non-carriers (OR=1.83; 95% CI 1.68-2.00).
- We detected significant positive correlation of ATM status with BC family history (p=1.8x10^-6).
- Within ATM PV carriers, we observed positive yet non-significant (at alpha <0.05) correlation between PRS and BC family history (p=0.10).
- After adjusting for multiple testing, we found no evidence of interaction of ATM status with clinical factors, or PRS with clinical factors within ATM PV carriers.

Figure 1. Remaining Lifetime Risk for ATM PV Carriers (N=216)

- The effect size of the PRS for stratification of ATM PV carriers was similar to that previously observed for non-carriers (Table 2).2
- In the independent cohort, 31.5% of ATM PV carriers were categorized as having low breast cancer risk (≤20%), 58.8% as moderate risk (20-50%), and 9.7% as high risk (>50%) (Figures 1 & 2).
- 44 women (20.4%) were re-categorized when comparing the ATM + Tyrer-Cuzick model to PRS + ATM + Tyrer-Cuzick (Figure 2).

Figure 2. Scatterplot of Lifetime Risk for ATM PV Carriers (N=216)

- In ATM PV carriers, our comprehensive model allowed for differentiation of ATM PV carriers into low, moderate, and high breast cancer risk categories.
- Precision breast cancer risk estimation may inform individualized clinical screening and prevention strategies.