Breast cancer risk management implications for families of ATM and CHEK2 mutation carriers

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BACKGROUND

- Inherited breast cancer may occur when gene mutations (e.g., BRCA1 and BRCA2) are passed down to offspring.
- Multi-gene panel testing is used to examine genes that are associated with hereditary cancers.
- ATM and CHEK2 are moderate penetrance breast cancer genes included in many multi-gene panel tests.
- Mutations in these genes confer a >20% lifetime breast cancer risk, which is the threshold for considering high-risk breast cancer screening.
- Cancer risks among ATM and CHEK2 carriers may vary based on family history of cancer and type of mutation.

OBJECTIVES

- To assess lifetime breast cancer risk among unaffected female first-degree relatives (FDR) and second-degree relatives (SDR) who are less than 80 years old and have a family member with a pathogenic or likely pathogenic ATM and/or CHEK2 mutation.
- To determine the impact of family history and gene positivity on breast cancer screening recommendations for at-risk first- and second-degree female relatives.

METHODS

- Clinical and family history data was collected from 56 ATM and 56 CHEK2 positive patients enrolled in the Inherited Cancer Registry (ICARE).
- Lifetime breast cancer risk was assessed for unaffected, female FDR and SDR through the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), which is a publicly available web-based computer program used to calculate lifetime risks of breast and ovarian cancer in women based on family history.
- Relatives were categorized based on breast cancer risk of < 20% versus ≥ 20%, given that national guidelines recommend screening through breast MRI when patients have a breast cancer risk of 20% or more. Relatives of individuals who carry the ATM mutation with a specific result of 7271T>G were excluded in this analysis given the higher breast cancer risks reported in the literature.

RESULTS

**CHEK2 FDR Lifetime Breast Cancer Risk Estimates (N= 103)**

- >20% 32 (31%)
- 15-19.9% 23 (22%)
- 10-14.9% 19 (18%)
- <10% 29 (28%)

**CHEK2 SDR Lifetime Breast Cancer Risk Estimates (N= 143)**

- >20% 58 (41%)
- 15-19.9% 25 (17%)
- 10-14.9% 43 (30%)
- <10% 17 (12%)

**ATM FDR Lifetime Breast Cancer Risk Estimates (N= 108)**

- >20% 25 (23%)
- 15-19.9% 37 (34%)
- 10-14.9% 44 (40%)
- <10% 21 (19%)

**ATM SDR Lifetime Breast Cancer Risk Estimates (N= 149)**

- >20% 38 (28%)
- 15-19.9% 39 (26%)
- 10-14.9% 44 (30%)
- <10% 25 (17%)

**Lifetime Breast Cancer Risk Estimates For Female First- and Second-Degree Relatives of CHEK2 and ATM Carriers**

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<thead>
<tr>
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<th>CHEK2 FDR (N = 103)</th>
<th>CHEK2 SDR (N = 143)</th>
<th>ATM FDR (N = 108)</th>
<th>ATM SDR (N = 149)</th>
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<tbody>
<tr>
<td>&gt;20%</td>
<td>23 (22%)</td>
<td>17 (12%)</td>
<td>37 (34%)</td>
<td>28 (19%)</td>
</tr>
<tr>
<td>&lt;20%</td>
<td>80 (78%)</td>
<td>126 (88%)</td>
<td>71 (66%)</td>
<td>121 (81%)</td>
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CONCLUSION

- BOADICEA calculates an individual's lifetime breast cancer risk solely off of their family history. Any additional risk factors are not included in this estimate.
- A pedigree may not specify FDR or SDR age, year of death, gender, and/or type of cancer. These factors play a large role in estimating lifetime breast cancer risk.
- Risks of individuals may be under or overestimated due to BOADICEA calculations based on age. Age is calculated up to age 80.

DISCUSSION

- Family history is an important factor in determining when testing for moderate penetrance breast cancer genes and high-risk breast cancer surveillance are indicated.
- Data indicates that cancer risk management based on ATM and CHEK2 positivity impacts FDR more than SDR.
- Some individuals who have a family member with a known ATM or CHEK2 mutation and have not yet undergone genetic testing may have a risk that exceeds 20% based on family history alone, thus testing positive for ATM or CHEK2 may not alter breast cancer surveillance recommendations.
- Computer-based breast cancer risk models can be beneficial tools to provide a general analysis of a family's lifetime breast cancer risk.

REFERENCES