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

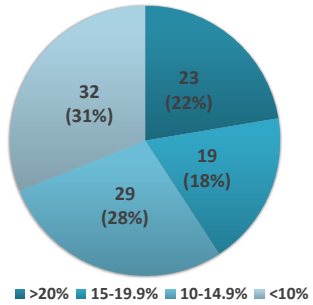
- To assess lifetime breast cancer risk among unaffected female first-degree relatives (FDR) and second-degree relatives (SDR) who are less than 80 years old and have a family member with a pathogenic or likely pathogenic *ATM* and/or *CHEK2* mutation.
- To determine the impact of family history and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

METHODS

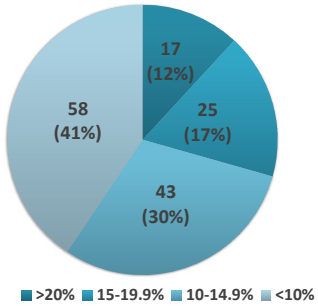
- Clinical and family history data was collected from 56 *ATM* and 56 *CHEK2* positive patients enrolled in the Inherited Cancer Registry (ICARE).
- Lifetime breast cancer risk was assessed for unaffected, female FDR and SDR through the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation 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

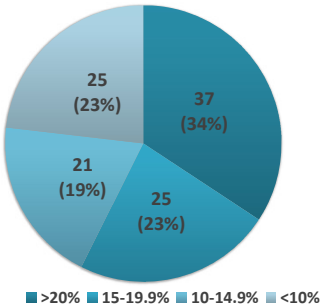
***CHEK2* FDR Lifetime Breast Cancer Risk Estimates (N= 103)**



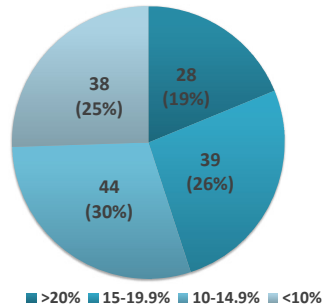
***CHEK2* SDR Lifetime Breast Cancer Risk Estimates (N= 143)**



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



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



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

	CHEK2		***ATM***	
	FDR (N = 103)	SDR (N = 143)	FDR (N = 108)	SDR (N = 149)
≥ 20%	23 (22%)	17 (12%)	37 (34%)	28 (19%)
< 20%	80 (78%)	126 (88%)	71 (66%)	121 (81%)

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

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