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Breast Cancer Screening Implications of Risk Modeling Among Female Relatives of *ATM* and *CHEK2* Carriers

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Abstract

Background—With increasing use of multi-gene panel tests, pathogenic and likely pathogenic (P/LP) variants are more frequently identified in the moderate-penetrance breast cancer genes *ATM* and *CHEK2*. Lifetime breast cancer risk among women with P/LP variants in these genes generally exceeds 20%, meeting the threshold at which high-risk breast cancer screening through breast magnetic resonance imaging (MRI) is recommended.

Methods—Among a registry-based sample of 56 *ATM* and 69 *CHEK2* carriers, we sought to determine the proportion of relatives in whom a P/LP variant would impact breast cancer surveillance. Lifetime breast cancer risks for unaffected, female first- and second-degree relatives were estimated using the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA).

Results—Among first-degree relatives of *ATM* and *CHEK2* carriers, only 22.6% and 14.9% had lifetime breast cancer risks ≥20% based on family cancer history alone; however, when including the proband's P/LP variant in the model, these proportions significantly increased to 56.6% and 55.3% ($p<0.0001$; $p<0.0001$). Similar increases in lifetime breast cancer risks were found among second-degree relatives.

Conclusions—These results suggest most female first- and second-degree relatives of *ATM* and *CHEK2* carriers do not qualify for breast MRI based on family cancer history alone; thus, testing for these genes, as well as awareness of positive moderate-penetrance breast cancer gene results in the family, may impact MRI eligibility. These findings highlight the potential utility of and need for breast cancer risk models that incorporate moderate-penetrance gene positivity to inform screening recommendations among at-risk family members.

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Keywords

ATM; *CHEK2*; Breast Cancer; Risk Assessment; Cancer Screening

Introduction

The identification of hereditary cancer has been revolutionized by next generation sequencing technoloiges through the use of multi-gene panel tests for inherited cancer predisposition. These tests have increased the identification of pathogenic and likely pathogenic (P/LP) variants in moderate-penetrance breast cancer susceptibility genes. Amongst the most commonly detected moderate-penetrance breast cancer genes are *ATM* and *CHEK2*.[1–3] It is estimated that the frequency in the general adult population of *ATM* heterozygotes is 1%,[4] with several hundreds of variants identified.[5] Based on a meta-analysis, the breast cancer risk for females heterozygous for *ATM* P/LP variants was estimated to be 6% by age 50 and 33% by age 80.[6] Similarly, the frequency of *CHEK2* heterozygotes in the European population was reported to be 1.2%.[7] The lifetime risk of breast cancer for females heterozygous for *CHEK2* P/LP variants has ranged from 20–44%, modified by family history of cancer.[8,9]

Screening guidelines for breast cancer are guided by estimates of lifetime breast cancer risk, with a threshold of ≥20% used to determine those for whom high-risk breast cancer screening is recommended through both mammogram and breast magnetic resonance imaging (MRI) per multiple national organizations.[10–12] Thus, individuals with a P/LP variant in *ATM* or *CHEK2* qualify for high-risk breast cancer screening given their risk exceeds the 20% threshold.

Among at-risk relatives of individuals with a P/LP variant in *ATM* or *CHEK2*, lifetime breast cancer risk estimates may be determined through models such as the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), using family history.[13] More recently, BOADICEA was updated to incorporate the data on P/LP variants in both *ATM* and *CHEK2* in the proband when estimating lifetime breast cancer risks among family members.[14]

Although testing for *ATM* and *CHEK2* are widely available, the potential for testing to impact breast cancer screening among at-risk family members beyond that based on family history alone remains incompletely defined. To address this gap, we sought to evaluate the following among unaffected, female first-degree relatives (FDRs) and second-degree relatives (SDRs) of probands with a P/LP variant in *ATM* or *CHEK2*: 1) compare lifetime breast cancer risks based on family cancer history alone versus with inclusion of the proband's *ATM* or *CHEK2* P/LP variant; 2) determine the proportion of at-risk female FDRs and SDRs in whom testing for a P/LP variant in *ATM* or *CHEK2* would impact breast cancer screening beyond that based on the risk assessment generated by BOADICEA; and 3) compare lifetime breast cancer risks among relatives of *ATM* carriers with relatives of *CHEK2* carriers.

Materials and Methods

Participants in the present study were drawn from the Inherited Cancer Registry (ICARE),[15] a research registry approved through the Vanderbilt University Institutional Review Board. ICARE was launched in summer 2010 to collect longitudinal data from patients interested in participating in inherited cancer research studies. Through ICARE enrollment, participants are consented and asked to complete a baseline questionnaire and an authorization for release of medical records to obtain relevant genetics records (i.e., genetic test reports and pedigrees). ICARE participants are recruited through various means including: 1) referrals from healthcare providers who have partnered with ICARE at various clinical centers across the United States and internationally; 2) directly online through the registry website (http://inheritedcancer.net); and 3) through local and national outreach activities.[16–18] Over 3000 participants are currently enrolled in ICARE, of which almost two-thirds have a P/LP variant in an inherited cancer predisposing gene.

Individuals enrolled in ICARE with a confirmed *ATM* or *CHEK2* P/LP variant who were aged 18 years or older and from unique families in whom a pedigree was available were included in the current analysis. Individuals excluded were: 1) double-heterozygous carriers with a P/LP variant in another established inherited breast cancer gene[11] in addition to *ATM* or *CHEK2*; 2) those with a relative identified to have a P/LP variant in another inherited breast cancer gene other than *ATM* or *CHEK2*; 3) those without any eligible FDRs or SDRs available for breast cancer risk estimation; 4) those with suspected mosaicism of the *ATM* variant, based on an allele frequency of <30% reported on the genetic testing laboratory report; and 5) those with the *ATM* c.7271T>G missense variant associated with a lifetime female breast cancer risk in the range of 60%.[19,20] The years of enrollment into ICARE covered February 2011 to May 2019.

Individuals enrolled in ICARE underwent genetic testing using a variety of commercial genetic testing laboratories at the discretion of their treating healthcare provider. Genetic testing criteria were determined by their treating healthcare provider and were not dictated by ICARE protocol. Clinical, demographic, and family history data were collected using ICARE questionnaires and medical records obtained using a signed authorization for release of medical records. Genetic test reports were reviewed to confirm carrier status. Pedigrees were reviewed to characterize personal and family history.

BOADICEA (BWA v4), which is designed for research use only and not intended to provide information on which to base clinical decisions, was used to calculate lifetime breast cancer risk based on family history data and the presence of a *CHEK2* or *ATM* P/LP variant in the proband, for all living, female FDRs and SDRs younger than age 80 without a diagnosis of breast, ovarian, and/or pancreatic cancer in whom their current age was recorded on the pedigree. Parents, full-siblings, and children were categorized as FDRs. Grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings were categorized as SDRs.

Demographic and clinical characteristics were summarized and compared between *ATM* and *CHEK2* carriers using Chi-square tests and Fisher's exact tests. Summary statistics of BOADICEA lifetime breast cancer risk estimates were generated for FDRs and SDRs based

on: 1) family cancer history alone; and 2) family cancer history and the proband's *ATM* or *CHEK2* P/LP variant. These risk estimates were compared using McNemar tests. Proportions of relatives with lifetime breast cancer risk estimates ≥20% were calculated. Risk estimates for FDRs were compared with SDRs within each carrier group using Chi-square tests. Risk estimates for relatives of *ATM* carriers were compared with relatives of *CHEK2* carriers using Chi-square tests. All statistical tests were considered significant at an alpha of 0.05.

Results

There were 56 *ATM* and 69 *CHEK2* confirmed P/LP variant carriers from unique families with a pedigree on file who met inclusion criteria for the analysis. Most *ATM* and *CHEK2* carriers were non-Hispanic White (89.1% and 95.7%) and female (94.6% and 98.6%) with a personal history of cancer (71.4% and 69.6%) and a family history of cancer (98.2% and 98.6%). Of those with a personal history of cancer, 75% of both *ATM* and *CHEK2* carriers had a personal history of breast cancer. Of those with a family history of cancer, 80% of *ATM* carriers and 75% of *CHEK2* carriers had a family history of breast cancer. Additional demographic and clinical data are shown in Table 1. No significant differences were noted across the two carrier groups in terms of clinical and demographic characteristics (all $p>0.05$).

Among the *ATM* carriers, current age was available for 106 unaffected, living female FDRs and 110 unaffected, living female SDRs. Based on family cancer history alone, 24 FDRs and 15 SDRs had a lifetime breast cancer risk ≥20%. Inclusion of the proband's *ATM* P/LP variant in the model significantly increased the number of FDRs and SDRs with a risk ≥20% to 60 and 31 ($p<0.0001$; $p<0.0001$) as shown in Table 2. There was not a significant difference in risk categorization between FDRs and SDRs when based on family cancer history alone ($p=0.085$); however, when the proband's *ATM* P/LP variant was included in the model, more FDRs had risks ≥20% compared with SDRs (56.6% versus 28.2%, respectively; $p<0.0001$).

Among the *CHEK2* carriers, current age was available for 141 unaffected, living female FDRs and 101 unaffected, living female SDRs. Based on family cancer history alone, 21 FDRs and 14 SDRs had a lifetime breast cancer risk ≥20%. Inclusion of the proband's *CHEK2* P/LP variant in the model significantly increased the number of FDRs and SDRs with a risk ≥20% to 78 and 22 ($p<0.0001$; $p=0.008$) as shown in Table 2. There was not a significant difference in risk categorization between FDRs and SDRs when based on family cancer history alone ($p=0.822$); however, when the proband's *CHEK2* P/LP variant was included in the model, more FDRs had risks ≥20% compared with SDRs (55.3% versus 21.8%, respectively; $p<0.0001$).

When comparing relatives of *ATM* carriers with relatives of *CHEK2* carriers, there was not a significant difference in the number of FDRs and SDRs who had a lifetime breast cancer risk ≥20% based on family cancer history alone ($p=0.118$ and $p=0.962$). Similar results were found upon including the proband's P/LP variant in the model ($p=0.841$and $p=0.284$).

Discussion

Our findings suggest that most at-risk female FDRs and SDRs of *ATM* and *CHEK2* carriers do not qualify for high-risk breast cancer screening based on family cancer history alone; however, there is a significant increase in the proportion of relatives who meet the 20% threshold for high-risk breast cancer screening when the proband's moderate-penetrance P/LP variant is included in the BOADICEA model, with more FDRs meeting the 20% threshold compared with SDRs. These results highlight the potential use of validated computer-based risk models that consider the effects of familial mutations in moderate-penetrance genes given the impact on breast cancer risk estimates, which inform breast cancer screening recommendations among at-risk relatives. Furthermore, these findings emphasize the importance of sharing moderate-penetrance genetic test results with at-risk relatives as awareness of such information by FDRs and SDRs could impact cancer screening and prevention strategies.

The use of BOADICEA in this study highlights the gap in other breast cancer risk estimation models, as BOADICEA is currently the only risk model to include the effects of moderate-penetrance *ATM* and *CHEK2* P/LP variants,[14] which are included in many multi-gene inherited cancer panel tests. With only 22.6% and 14.9% of *ATM* and *CHEK2* carrier FDRs with a lifetime breast cancer risk ≥20% based on family cancer history alone and similar results among SDRs (13.6% among *ATM* carriers and 13.9% among *CHEK2* carriers), our results suggest that most at-risk female FDRs and SDRs of *ATM* and *CHEK2* carriers do not qualify for high-risk breast cancer screening through breast MRI based on family cancer history alone. Yet when including the proband's P/LP variant in the risk model, the proportion of relatives with a lifetime breast cancer risk ≥20% significantly increased. These findings suggest that awareness and inclusion of a previously identified first- or second-degree relative's *ATM* or *CHEK2* P/LP variant in computer-based risk modeling may impact a patient's breast MRI eligibility. This highlights the potential usefulness of and need for a clinically-validated risk model that takes into account moderate-penetrance P/LP variants in the family when estimating breast cancer risk in at-risk relatives.

Using the Tyrer-Cuzick risk model, a multi-center prospective study of *BRCA1/2*-negative individuals found that among 11 *ATM* carriers and 15 *CHEK2* carriers, the proportion of families in which a positive genetic test result would enhance breast cancer screening recommendations among an at-risk, living FDR was 54.5% (6 of 11) and 30.8% (4 of 13), respectively.[21] Our study, which included a larger sample size and utilized the BOADICEA risk model, found a greater proportion of *ATM* and *CHEK2* carrier families in which a positive result would alter breast cancer screening among at least one at-risk, living FDR (75% and 83%, respectively). Our analysis also found no significant difference in lifetime breast cancer risk estimates between *ATM* and *CHEK2* carrier relatives (all $p>0.05$), suggesting that similar proportions of such moderate-penetrance carrier families would benefit from predictive genetic testing.

While there is value for at-risk relatives to incorporate familial *ATM* and *CHEK2* P/LP variants when determining breast cancer risk, it still remains important for these family members to consider genetic testing themselves. Determining their own mutation status has

the potential to provide improved breast cancer screening recommendations beyond that recommended based on family cancer history and known familial P/LP variants alone. Consequently, efforts to improve dissemination of information regarding sharing genetic test results across families and the need for subsequent genetic testing among family members remain critical to maximize benefits based on results while avoiding over screening.

The current study has several strengths including: 1) the high-risk, registry-based design through which *ATM* and *CHEK2* carriers were recruited; 2) confirmation of genetic test results; and 3) availability of pedigrees on all participants. Despite these strengths, there remain limitations, including limited sample size and lack of data on other breast cancer risk factors, such as hormone receptor status or lifestyle factors, among at-risk relatives in whom breast cancer estimates were conducted; thus, risk estimates for relatives may differ when using models that include these other well-established breast cancer risk factors.

In summary, our findings highlight that risk models may be valuable tools in informing at-risk, female FDRs and SDRs how genetic testing for moderate-penetrance genes could impact breast cancer screening. For instance, relatives who have not undergone genetic testing for a known familial *ATM* or *CHEK2* mutation may already have a lifetime risk of breast cancer that exceeds 20%; thus, genetic test results may not alter breast cancer surveillance. Our data also suggest that a thorough review of family history in addition to utilization of computer-based cancer risk models that include familial moderate-penetrance breast cancer gene results may help healthcare professionals frame a discussion with at-risk relatives around the clinical utility of predictive testing for P/LP variants in moderate-penetrance genes. Furthermore, we have underscored the importance of sharing positive moderate-penetrance gene results with at-risk relatives as this information may alter surveillance recommendations. Prior efforts have eloquently highlighted issues surrounding the lack of understanding about utility of testing and management for moderate-penetrance genes;[22] thus, our study contributes data to quantify the impact of positive test results in moderate-penetrance genes on familial breast cancer risk. Ultimately, larger prospective cohort studies are needed to evaluate the impact of risk model estimates on breast cancer screening recommendations and decision-making and to further inform the clinical utility of identifying moderate-penetrance P/LP variants.

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Table 1:

Characteristics of *ATM* and *CHEK2* heterozygotes

	ATM N=56		*CHEK2* N=69		*P*
	n	**%**	**n**	**%**	
Female	53	94.6%	68	98.6%	0.324
Non-Hispanic White [a]	49	89.1%	66	95.7%	0.183
Has children	45	80.4%	57	82.6%	0.747
Personal history of cancer	40	71.4%	48	69.6%	0.820
Personal history of breast cancer	30	53.6%	36	52.2%	0.876
Family history of cancer [b]	55	98.2%	68	98.6%	1
Family history of breast cancer [b]	44	78.6%	51	73.9%	0.544

[a] Excludes 1 unknown *ATM* heterozygote; percent reported is out of N=55

[b] Presence of cancer among first- and/or second-degree relatives as shown on the available pedigree

Table 2:

Lifetime breast cancer risk estimates of female relatives of *ATM* and *CHEK2* carriers

				Based on family cancer history and inclusive of the proband's P/LP variant	
				<20%	**≥20%**
Relatives of *ATM* Carriers	Based on family cancer history alone	First-degree relatives (N=106)	<20%	46 (43.4%)	36 (34.0%)
			≥20%	0 (0.0%)	24 (22.6%)
		Second-degree relatives (N=110)	<20%	79 (71.8%)	16 (14.5%)
			≥20%	0 (0.0%)	15 (13.6%)
Relatives of *CHEK2* Carriers	Based on family cancer history alone	First-degree relatives (N=141)	<20%	63 (44.7%)	57 (40.4%)
			≥20%	0 (0.0%)	21 (14.9%)
		Second-degree relatives (N=101)	<20%	79 (78.2%)	8 (7.9%)
			≥20%	0 (0.0%)	14 (13.9%)