original reports

Association of Family Cancer History With Pathogenic Variants in Specific Breast Cancer Susceptibility Genes

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abstract

PURPOSE Family cancer history is an important component of genetic testing guidelines that estimate which patients with breast cancer are most likely to carry a germline pathogenic variant (PV). However, we do not know whether more extensive family history is differentially associated with PVs in specific genes.

METHODS All women diagnosed with breast cancer in 2013-2017 and reported to statewide SEER registries of Georgia and California were linked to clinical genetic testing results and family history from two laboratories. Family history was defined as strong (suggestive of PVs in high-penetrance genes such as *BRCA1/2* or *TP53*, including male breast, ovarian, pancreatic, sarcoma, or multiple female breast cancers), moderate (any other cancer history), or none. Among established breast cancer susceptibility genes (*ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CDH1*, *CHEK2*, *NF1*, *PALB2*, *PTEN*, *RAD51C*, *RAD51D,* and *TP53*), we evaluated PV prevalence according to family history extent and breast cancer subtype. We used a multivariable model to test for interaction between affected gene and family history extent for *ATM*, *BRCA1/2*, *CHEK2,* and *PALB2*.

RESULTS A total of 34,865 women linked to genetic results. Higher PV prevalence with increasing family history extent ($P < .001$) was observed only with *BRCA1* (3.04% with none, 3.22% with moderate, and 4.06% with strong history) and in triple-negative breast cancer with *PALB2* (0.75% with none, 2.23% with moderate, and 2.63% with strong history). In a multivariable model adjusted for age and subtype, there was no interaction between family history extent and PV prevalence for any gene except *PALB2* ($P = .037$).

CONCLUSION Extent of family cancer history is not differentially associated with PVs across established breast cancer susceptibility genes and cannot be used to personalize genes selected for testing.

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INTRODUCTION

Germline genetic testing is common after a breast cancer diagnosis,[1] and may increase further as germline-targeted therapies emerge.[2,3] Recent studies have defined the prevalence and penetrance of pathogenic variants (PVs) in several cancer susceptibility genes among population-based breast cancer patients.[4,5] However, testing multiple genes substantially increases the yield of uncertain (variant of uncertain significance [VUS]) results, particularly among groups that have had limited testing access such as racial/ethnic minorities.[3,6] VUS results may contribute to anxiety and suboptimal treatment recommendations.[7,8] Thus, there is rationale for careful consideration of which genes to test.

Family cancer history is an important component of genetic testing guidelines that aim to identify which patients are most likely to carry a PV.[9] More extensive family history (eg, more relatives diagnosed with cancer or at younger ages) has been associated with

higher PV prevalence in high-penetrance genes such as *BRCA1* and *BRCA2* (*BRCA1/2*).[10] Yet, we do not know whether family cancer history is differentially associated with specific PVs: for example, whether more extensive family cancer history predicts a PV in *BRCA1* but not the lower-penetrance *ATM*. A better understanding of the relationship between family cancer history and the prevalence of PVs in different genes might inform selection of a smaller, more personalized testing panel for each patient. We examined the association between family cancer history and PV prevalence by gene among a population-based cohort of women diagnosed with breast cancer from 2013 to 2017. Our hypothesis was that PVs in moderate-penetrance breast cancer genes such as *ATM*, *CHEK2*, and *PALB2* would be less associated with the extent of family cancer history than PVs in high-penetrance genes such as *BRCA1/2*. If confirmed, such a finding would suggest that patients who have a family cancer history that is most consistent with a high-penetrance gene PV might be spared testing of

CONTEXT

Key Objective

Can we use family cancer history to select genes for germline testing in women with breast cancer?

Knowledge Generated

Among 34,865 female patients with breast cancer who underwent clinical germline genetic testing, there was no substantial difference between the established breast cancer genes (ATM, BARD1, BRCA1, BRCA2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C, RAD51D, and TP53) in association of the extent or type of family cancer history with carrying a pathogenic variant.

Relevance

Family cancer history cannot be used to select specific genes for germline testing in women with breast cancer.

moderate-penetrance genes—and the higher probability of a VUS result that comes with testing more genes.[3,6]

METHODS

All women diagnosed with breast cancer from January 1, 2013, to December 31, 2017, in Georgia or California and reported to SEER cancer registries in Georgia (the Georgia Cancer Registry) and in California (the Los Angeles Cancer Surveillance Program, the Greater Bay Area Cancer Registry, and the Cancer Registry of Greater California) were linked to clinical germline genetic testing results from four laboratories (Ambry Genetics, Aliso Viejo, CA; GeneDx, Gaithersburg, MD; Invitae, San Francisco, CA; and Myriad Genetics, Salt Lake City, UT) that performed the substantial majority of testing according to clinician and patient surveys.[1,11] Two of these laboratories (Ambry Genetics and Myriad Genetics), comprising 75% of tested patients, had previously abstracted the family cancer history reported on testing request forms by ordering clinicians for research use,[12,13] and only patients who linked to a test from one of these two laboratories were included for analysis. For a subset of women who participated in the earlier iCanCare study,[14] patient self-reported family cancer history was compared with that provided by laboratories. All research was approved by institutional review boards associated with the SEER registries.

As previously described,[1,3,8,11] the analytic data set combined genetic results with demographic and clinical variables from SEER registries. The results were reported by gene with the interpretation provided to the ordering clinician, as follows: PV or likely PV; VUS; and benign or likely benign. We focused on genes associated with breast cancer risk in the CARRIERS and Breast Cancer Association Consortium studies[4,5]: *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *CDH1*, *CHEK2*, *NF1*, *PALB2*, *PTEN*, *RAD51C*, *RAD51D*, and *TP53*.

Family cancer history was provided in terms of degree (first-degree relative [FDR] or second-degree relative), number and sex of affected relative/s, and their cancer diagnoses. On the basis of testing guidelines and our prior work,[9,14] we categorized the extent of family cancer history as strong (male FDR/second-degree relative with breast cancer; FDR with sarcoma, pancreatic, or ovarian cancer; two or more female FDRs with breast cancer; three or more FDRs with any cancer), moderate (any family cancer history not categorized as strong), or none. This definition of strong family cancer history was based on features that are associated with PVs in high-penetrance genes (*BRCA1/2* for male breast, pancreatic, and ovarian cancer; *TP53* for sarcoma) and that are recognized by practice guidelines as indications for genetic testing.[9] As a sensitivity analysis, we evaluated the effect of categorizing family cancer history in a manner more focused on breast cancer, given that all tested patients had a breast cancer diagnosis. In this alternative categorization, family cancer history was defined as follows: any relative with breast cancer, but no relatives with any other cancer (breast cancer only); any relative with a nonbreast cancer, but none with breast cancer (nonbreast cancer only); relatives with breast cancer and with nonbreast cancers (in different individuals); and no family cancer history.

We evaluated PV prevalence by gene according to family cancer history extent and breast cancer subtype (hormone receptor–negative and human epidermal growth factor receptor 2–negative [triple-negative] *v* non–triple-negative), given differential PV prevalence by subtype.[4,5] We used a multivariable model of PV prevalence, controlling for diagnosis age and subtype, to test for interaction between five genes in which PVs are relatively common (*BRCA1/2*, *ATM*, *CHEK2*, and *PALB2*) and extent of family cancer history.

RESULTS

A total of 34,865 women linked to genetic results. Among these, 1,016 (2.9%) had previously reported their family cancer history as a component of their participation in the earlier iCanCare study,[14] and this prior report enabled us to compare self-reported to laboratory-reported family cancer history. For a reported family history of any relative affected by cancer (*v* no relatives affected), the concordance between self-report and laboratory report was 95% (Fleiss kappa = 0.903).

Table 1 shows patient characteristics; family cancer history was missing for approximately 15%-20%, with no pattern

TABLE 1. Characteristics of Women With Breast Cancer by Family Cancer History[a]

Characteristic	No Family History	Moderate Family History	Strong Family History	Not Reported
Age, years, No. (%)				
< 50	8,951 (48)	5,743 (31)	1,415 (8)	2,659 (14)
50-64	3,213 (23)	5,578 (39)	3,331 (23)	2,131 (15)
65-74	912 (16)	2,079 (35)	1,991 (34)	897 (15)
> 74	222 (11)	616 (31)	814 (41)	324 (16)
Race or ethnicity, No. (%)				
Non-Hispanic White	7,170 (28)	9,416 (37)	5,250 (21)	3,654 (14)
Black	1,644 (36)	1,501 (33)	834 (18)	611 (13)
American Indian/Alaska Native	39 (32)	36 (30)	18 (15)	29 (24)
Asian or Pacific Islander	1,703 (40)	1,239 (29)	575 (14)	735 (17)
Hispanic	2,653 (44)	1,714 (28)	821 (14)	865 (14)
Unknown	89 (32)	110 (39)	53 (19)	30 (11)
Neighborhood socioeconomic status, No. (%), %				
< 10 poverty	6,051 (31)	6,895 (35)	3,611 (18)	3,125 (16)
10-19 poverty	4,260 (30)	4,447 (32)	2,438 (17)	2,853 (20)
> 19 poverty	2,969 (37)	2,653 (33)	1,486 (18)	956 (12)
Breast cancer stage, No. (%)				
0	1,640 (32)	2,118 (42)	1,231 (24)	109 (2)
I	4,456 (28)	5,564 (35)	3,275 (21)	2,584 (16)
II	4,657 (35)	4,185 (32)	2,086 (16)	2,297 (17)
III	1,680 (38)	1,400 (32)	581 (13)	719 (16)
IV	536 (38)	450 (32)	223 (16)	215 (15)
Breast cancer grade, No. (%)				
1	1,835 (26)	2,539 (35)	1,514 (21)	1,291 (18)
2	5,050 (30)	5,578 (33)	3,199 (19)	2,943 (18)
3	5,713 (36)	5,038 (32)	2,405 (15)	2,792 (18)
Breast cancer subtype, No. (%)				
ER/PR-positive, HER2-negative	6,851 (30)	7,737 (33)	4,438 (19)	4,106 (18)
HER2-positive, any ER/PR status	2,253 (36)	2,017 (33)	937 (15)	968 (16)
ER/PR/HER2-negative (triple-negative)	2,093 (38)	1,710 (31)	743 (14)	904 (17)
State, No. (%)				
California	9,822 (32)	10,317 (34)	5,526 (18)	4,593 (15)
Georgia	3,476 (33)	3,699 (36)	2,025 (19)	1,212 (12)
Year of diagnosis, No. (%)				
2013	3,638 (38)	3,101 (33)	1,581 (17)	1,162 (12)
2014	2,848 (32)	2,902 (33)	1,576 (18)	1,566 (18)
2015	2,831 (31)	3,217 (35)	1,678 (18)	1,428 (16)
2016	2,391 (30)	2,930 (37)	1,532 (20)	1,070 (13)
2017	1,590 (24)	1,866 (28)	1,084 (16)	2,227 (33)

Abbreviations: ER, estrogen receptor; FDR, first-degree relative; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

[a]Strong family cancer history was defined as: male FDR or second-degree relative with breast cancer; FDR with sarcoma, pancreatic, or ovarian cancer; two or more female FDRs with breast cancer; or three or more FDRs with any cancer. Moderate family cancer history was defined as any family history of cancer not characterized as strong. Family cancer history was derived from laboratory report and validated among a subset of 1,016 women who had previously self-reported their family cancer history; for any family cancer history versus none, concordance between self-report and laboratory report was 95% (Fleiss Kappa = 0.903).

TABLE 2. Pathogenic Variant Prevalence (%) by Family Cancer History,[a] Gene, and Breast Cancer Subtype

Family History	No.	BRCA1	BRCA2	ATM	BARD1	CDH1	CHEK2	NF1	PALB2	PTEN	RAD51C	RAD51D	TP53
All patients													
None	11,197	3.04[b]	2.83	0.90	0.29	0.09	1.70	0.05	0.77	0.09	0.26	0.16	0.38
Moderate	11,464	3.22[b]	3.32	1.07	0.25	0.08	2.08	0.17	1.14	0.05	0.18	0.14	0.30
Strong	6,118	4.06[b]	3.81	1.15	0.37	0.21	2.37	0.06	1.17	0.09	0.25	0.20	0.36
Tested for gene		28,614	28,631	18,188	17,557	19,175	18,194	6,582	18,694	19,272	17,600	17,473	19,317
Triple-negative breast cancer subtype													
None	2,093	9.19[b]	3.89	0.26	0.62	0.08	0.60	0.00	0.75[b]	0.08	0.62	0.27	0.32
Moderate	1,710	12.13[b]	4.22	0.28	0.47	0.09	0.64	0.50	2.23[b]	0.09	0.76	0.19	0.09
Strong	743	17.34[b]	5.97	0.83	1.27	0.20	0.62	0.00	2.63[b]	0.39	1.05	0.85	0.39
Tested for gene		4,526	4,484	2,738	2,663	2,887	2,743	924	2,816	2,898	2,669	2,654	2,904
Non–triple-negative breast cancer subtypes[c]													
None	9,104	1.63[b]	2.58	1.04	0.21	0.09	1.95	0.06	0.78	0.09	0.18	0.14	0.39
Moderate	9,754	1.65[b]	3.17	1.21	0.21	0.07	2.32	0.12	0.96	0.04	0.08	0.13	0.33
Strong	5,375	2.22[b]	3.52	1.19	0.25	0.21	2.59	0.07	0.98	0.05	0.14	0.11	0.36
Tested for gene		24,088	24,147	15,450	14,894	16,288	15,451	5,658	15,878	16,374	14,931	14,819	16,413

Abbreviations: ER, estrogen receptor; FDR, first-degree relative; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

[a]Strong family cancer history was defined as: male FDR or second-degree relative with breast cancer; FDR with sarcoma, pancreatic, or ovarian cancer; two or more female FDRs with breast cancer; or three or more FDRs with any cancer. Moderate family cancer history was defined as any family history of cancer not characterized as strong. Family cancer history was derived from laboratory report and validated among a subset of 1,016 women who had previously self-reported their family cancer history; for any family cancer history versus none, concordance between self-report and laboratory report was 95% (Fleiss Kappa = 0.903).

[b]Prevalence varies significantly with family history ($P < .05$).

[c]Non–triple-negative subtypes consisted of ER- and/or PR-positive and HER2-negative disease and HER2-positive disease with any ER/PR status.

except a higher rate in 2017 (33%) than in earlier years (12%-18%). A report of no family cancer history was more common among Black (36%), Asian or Pacific Islander (40%), and Hispanic (44%) patients than among non-Hispanic White (28%) patients.

Table 2 shows PV prevalence by family cancer history, gene, and subtype. Higher prevalence with increasing extent of family cancer history ($P < .001$) was observed with BRCA1 (among all patients: 3.04% with none, 3.22% with moderate, and 4.06% with strong family cancer history) and PALB2 (among patients with triple-negative breast cancer: 0.75% with none, 2.23% with moderate, and 2.63% with strong family cancer history).

Figure 1 shows adjusted PV prevalence by gene and family cancer history. In a model of PV prevalence by gene, adjusted for diagnosis age and breast cancer subtype, there was no interaction between extent of family cancer history and PV prevalence for any gene except PALB2 with moderate family cancer history ($P = .037$).

In our sensitivity analysis of using a breast cancer–focused categorization of family cancer history, the distribution of patients with a family cancer history of both breast and nonbreast cancers (Data Supplement) was similar to the distribution of patients with a family cancer history that we categorized as strong (Table 1). In the Data Supplement,

higher PV prevalence with increasing extent of family cancer history ($P < .05$) was observed for BRCA1, BRCA2, PALB2, and RAD51C. However, in a multivariable model of PV prevalence by gene, adjusted for diagnosis age and breast cancer subtype (Data Supplement), there was no significant interaction between extent of family cancer history and PV prevalence for any gene except PALB2 ($P = .012$). These modeling results were consistent with those presented in Figure 1, in which we used the strong/moderate categorization of family cancer history.

DISCUSSION

Among 34,865 patients with breast cancer, we found minimal evidence that the extent of family cancer history is differentially associated with PVs across breast cancer susceptibility genes. Although we used a definition of strong family cancer history (eg, male breast cancer and ovarian cancer) on the basis of testing guidelines that were developed primarily for BRCA1/2, PV distribution by family cancer history was fairly uniform in other genes. In a sensitivity analysis that categorized family cancer history differently, as breast cancer versus nonbreast cancer, we obtained very similar results. We conclude that the extent of family cancer history cannot be used to exclude any established breast cancer susceptibility gene (BRCA1, BRCA2, ATM, BARD1, CDH1, CHEK2, NF1, PALB2,

FIG 1. Adjusted pathogenic variant prevalence by affected gene and family cancer history. Marginal distributions from multivariable logistic model, including family cancer history, subtype, and age as covariates. A statistically significant interaction ($P < .05$) between family cancer history and gene was seen only for *PALB2*.
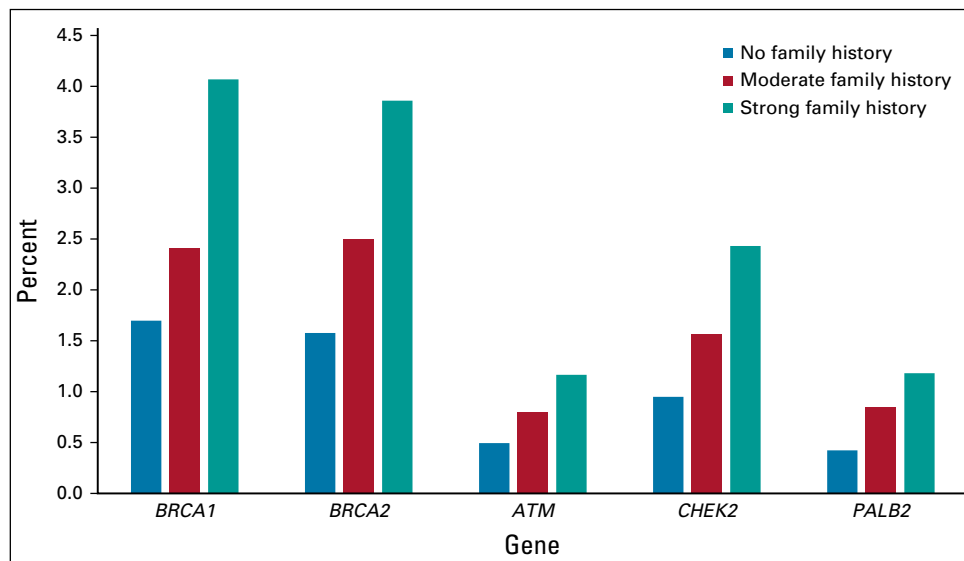
PTEN, RAD51C, RAD51D, and *TP53*) from testing in a woman with breast cancer. This finding is robust to differences in how family cancer history is categorized.

Notably, racial/ethnic minority patients were more likely than non-Hispanic White patients to have a report of no family cancer history. Potential explanations for this difference might include deficits in family history-taking by clinicians, which would be consistent with known racial/ethnic disparities in hereditary risk assessment referrals and genetic testing receipt,[11,15] and/or higher competing mortality risks related to social determinants of health. Prior work has shown that limited family structure (eg, less information about cancer patterns in a family because of small family size or early deaths from other causes) can lead clinicians to underestimate the likelihood of *BRCA1/2* PV carriage,[16] and this may warrant consideration when evaluating diverse patients and families for cancer genetic testing.

Study limitations include family cancer history collection from genetic test request forms rather than patient self-report; however, there was high concordance with self-reported family cancer history in a subset of patients for whom self-report was available,[14] consistent with prior work.[12] Patients were tested clinically, and thus may not represent untested patients; they resided in two states, which may not represent the entire United States. These limitations are balanced by notable strengths, including a diverse, contemporary sample from population-based SEER registries and detailed genetic results from testing laboratories.

Questions remain about the clinical utility of detecting PVs in lower-penetrance genes such as *ATM* and *CHEK2*, with uncertainty about optimal breast screening regimens and no gene-specific evidence as yet to support risk-reducing surgery or targeted therapies.[9,17-19] Thus, we recommend pretest counseling about the advantages and disadvantages of including lower-penetrance genes. However, the extent of family cancer history should not be used to estimate that a patient will test positive for a PV in one breast cancer susceptibility gene versus another.

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DISCLAIMER

The ideas and opinions expressed herein are those of the author(s) and do not necessarily reflect the opinions of the State of California, Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their contractors and subcontractors.

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