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The burden of breast cancer predisposition variants across the age spectrum among 10,000 patients

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Abstract

Background/Objectives: Women diagnosed with breast cancer at an older age are less likely to undergo genetic cancer risk assessment and genetic testing since the guidelines and referrals are

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biased toward earlier age at diagnosis. Thus, we determined the prevalence and type of pathogenic cancer predisposition variants among women with a history of breast cancer (BC) diagnosed at age 65 vs. <65 years.

Design: Prospective registration cohort.

Setting: The Clinical Cancer Genomics Community Research Network, including 40 community-based clinics in the US and 5 in Latin America.

Participants: Women with BC and genetic testing results.

Measurements: Socio-demographic characteristics, clinical variables and genetic profiles were compared between women aged 65 and <65 years at BC diagnosis.

Results: Among 588 women diagnosed with BC 65 years of age and 9,412 diagnosed <65 years, BC associated pathogenic variants (PVs) were detected in 5.6% of those 65 (n=33) and 14.2% of those <65 years (n=1,340) ($p < 0.01$). PVs in high-risk genes (e.g., *BRCA1*, *BRCA2*) represented 81.1% of carriers among women 65 years (n=27), and 93.1% of those < 65 years (n=1248), ($p=0.01$). *BRCA2* PVs represented 42.4% of high-risk gene findings for those 65 years, whereas *BRCA1* PVs were most common among carriers <65 years (49.7%). PVs (n=7) in moderate-risk genes represented 21.2% for carriers 65 and 7.3% of those <65 (n=98; $p<.01$). *CHEK2* PVs were the most common moderate-risk gene finding in both groups.

Conclusion: Clinically actionable BC susceptibility PVs, particularly in *BRCA2* and *CHEK2*, were relatively prevalent among older women undergoing genetic testing. The significant burden of PVs for older women with BC provides a critical reminder to recognize the full spectrum of eligibility and provide genetic testing for older women, rather than exclusion based on chronological age alone.

Keywords

Breast cancer; genetics; older women

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women globally.¹ In the United States alone, an estimated 252,710 of new invasive breast cancer cases were diagnosed in 2017, of which more than 50% were diagnosed in women older than 60 years, making breast cancer a disease of aging.² Moreover, the population aged 65 years and over is projected to more than double by 2050, which will be associated with a projected rise in breast cancer incidence driven by the association of cancer and aging.^{3–5}

Approximately 10% of all breast cancers are associated with genetic predisposition.^{6,7} Identification of inherited breast cancer-associated pathogenic variants (PVs) is important, since this may influence cancer treatment and surveillance for the individual, and it enables cascade genetic testing, and cancer screening and prevention for family members.⁸ The genes most commonly associated with breast cancer are *BRCA1* and *BRCA2*, followed by *PALB2*, *TP53*, *CHEK2*, and *ATM*.⁹ As outlined in the National Comprehensive Cancer Network (NCCN) guidelines, breast cancer risk-assessment and management depends on the

gene and PV found.⁷ Genetic testing has traditionally been indicated in patients with breast cancer with characteristics predicting a higher probability of being a carrier, generally early age at diagnosis (<age 50), or triple negative breast cancer (TNBC) younger than age 60 and/or those with a personal or family history of multiple cancers.⁷ Though the guidelines have evolved to be progressively more inclusive over time (e.g., single case age limit up to 50 years rather than 45 if there is limited family structure¹⁰; TNBC up to age 60 years^{11,12}; recommending *TP53* testing for *BRCA*-negative BC patients ≥30 years old¹³), there has been less focus on the growing population of older breast cancer survivors. Most insurers and MediCare only cover genetic testing for individuals who meet the NCCN guidelines.

The lack of information on the role of genetic testing among older women with breast cancer stems from the low inclusion of older patients in genetic studies, mirroring what is seen in other aspects of cancer research^{5,14–16}. An earlier study of a smaller cohort (n = 488) that explored the landscape of breast cancer susceptibility genes up to age 60 years demonstrated 6.4% deleterious mutations among 109 unselected patients aged >60, compared to 7.5% among those aged 46–60¹⁷. Most other studies were wholly or largely younger individuals because older women seldom undergo genetic testing in everyday clinical practice.

The aim of this study was to determine the prevalence and type of PVs among a larger sample of women with breast cancer diagnosed at age ≥65 who received genetic testing in community-based clinics, and to compare their clinical and genetic profiles to women younger than 65 years at breast cancer diagnosis.

METHODS

Study Population

The study population was obtained from the Clinical Cancer Genomics Community Research Network (CCGCRN) cohort, eligibility for which includes any individual receiving genetic cancer risk assessment (GCRA) at cancer centers and community-based clinics from 40 sites in the US and 5 sites in Latin America (LA).^{9,18,19} All women enrolled in the CCGCRN with a diagnosis of breast cancer (invasive or ductal carcinoma in situ) and receiving GCRA from 1997 to 2016 were included in this analysis. Women were divided into two groups according to their age at breast cancer diagnosis (≥65 and <65 years). We used the older age definition recommended by the United Nations.¹¹ Informed consent was obtained from all participants and the institutional ethics review board at each institution approved the study protocol.

Data collection

Sociodemographic characteristics, clinical variables, multi-generational pedigrees and genetic profiles were obtained from the CCGCRN database. Demographic data and five generation pedigrees were obtained at the time of enrollment, including family history of cancer. Genetic testing was performed utilizing various methods, and depended on availability of specific gene tests in that era, and each institution's practice. Testing exclusively for *BRCA1* and *BRCA2* occurred between 1996–2013, expanding to multi-gene

panel tests (MGPT) that included other high-risk breast cancer-associated genes (*CDH1*, *PALB2*, *PTEN*, *TP53*, *STK11*) and moderate-risk genes (*CHEK2*, *ATM*, *NF1*, *NBN*).^{9,19–23}

Statistical Analysis

Data are presented as medians, means or proportions. Descriptive statistics were utilized to analyze clinical and demographic characteristics, while Fisher's and chi-squared test statistics were used to compare groups. A two-sided p value of < 0.05 was considered statistically significant. XLSTAT software version 2017.6 was used for statistical calculations.

RESULTS

A total of 10,000 women with a history of breast cancer were identified from the CCGCRN registry database. Of those, 9,412 were <65 years at breast cancer diagnosis (the younger group), and 588 women were aged ≥ 65 years (the older group) (Figure 1). All participants had testing that included *BRCA1* and *BRCA2* (*BRCA*); 54% (n=318) of older women and 37% (n=3493) of younger women had MGPT; 46% (n=270) and 63% (n=5919) had *BRCA* testing alone, respectively (p< 0.01).

A PV in a breast cancer predisposition gene was detected in 5.6% of older women (33 women, one with two variants) and 14.2% of their younger counterparts (n=1,340 women with 1,346 variants total) (p < 0.01) (Figure 1). Among the breast cancer related variants in older women, 81.8% (n=27) were high risk, compared with 93.1% of those in younger women (n=1248) (p =0.01) (Table 1). *BRCA2* was the most frequent high-risk gene with a PV among older women, representing 42.4% of cases (n=14), followed by *BRCA1* (30.3%, n=10), and *PALB2* (9.0%, n=3). The distribution of high-risk genes with a PV in younger women was *BRCA1* (49.7%, n=666), *BRCA2* (35%, n=469), *PALB2* (5.0%, n=68), *TP53* (2.6%, n =36) and *PTEN* (<1%, n=9). The proportion of PVs in moderate-risk genes was higher in older women (21.2% [n=7] vs 7.3%, [n=98]; p=0.01). Among older women with PVs in moderate-risk genes, *CHEK2* (15.1%, n=5) was most prevalent, followed by *ATM* (3.0%, n=1). *CHEK2* represented a smaller proportion of cases among younger women (4.8% vs 15.1%; p=0.02), though the frequency of *ATM* was similar in both groups (2.0%, n=27; p 0.50). A PV in *TP53* was detected in one older woman, but review of her clinical status indicated the presence of chronic lymphocytic leukemia, marking this as somatic interference (aberrant clonal expansion of blood cells with an acquired *TP53* abnormality, rather than a germline finding)²⁴, so the case was included in the non-carrier group.

Older women with breast cancer associated PVs were less likely to present with advanced stage (IIB–IV) breast cancer compared to their younger counterparts (OR 0.51; 95% CI 0.29–0.90 [12.5% vs 42%]; p<0.01). We found no difference in tumor estrogen- or progesterone-receptor expression (ER/PR + 64% vs 54.3%; p 0.41) between older and younger carriers, respectively. Though prevalent in both groups, older carriers more frequently had first degree relatives with history of breast or ovarian cancer than younger carriers (79.4% vs 54.4%; p<0.01). The proportion of cases with new primary breast cancers (14.7% vs 19.1%; p 0.66) or Ashkenazi Jewish ancestry (8.8% vs 5.7%; p 0.44) was similar between older and younger carriers. In addition, older women with PVs had fewer estrogen

and/or progesterone receptor (ER/PR) positive tumors (64% vs 80%, $p = 0.07$) when compared to older non-carrier women. (Table 2)

DISCUSSION

In this study we report the frequency and spectrum of PVs in breast cancer-susceptibility genes in a large cohort of 10,000 patients, including more than five hundred older women undergoing GCRA and genetic testing. Overall, 5.6% ($n=33$) of older women with breast cancer in our cohort carried a breast cancer-associated germline PV. This frequency of PVs is higher than reported in population databases ($\sim 1.7\%$)⁹, and comparable to the 6.4% ($n=7$) rate reported by Tung et al¹⁷ among a smaller ($n=109/488$) series of breast cancer patients age > 60 years. Both of our studies highlight the relatively higher proportion of moderate risk gene PVs among the older patients. This study provides evidence that older women with breast cancer have a meaningful probability of carrying a breast cancer-susceptibility gene PV, and suggests that they and their families may benefit from access to GCRA in clinical practice.

BRCA2 was the most frequent high-risk gene PV among older women in our study, while *BRCA1* was most frequent among the younger population. Both *BRCA1* and *BRCA2* confer a substantial risk of new primary breast and ovarian cancers. Risk-reducing salpingo-oophorectomy and high-risk breast screening should be considered for older patients with an adequate life expectancy.⁷ PVs in other high-risk genes were rare in the older cohort. However, moderate-risk PVs were more frequent among older women, with *CHEK2* being the most common PV regardless of age. Interestingly, the proportion of *CHEK2* PVs found among older women in our study (15.1%) is higher than previous reports, which vary from 1 to 5% depending on the population studied.⁹ However, our results are consistent with a recent study on the age distribution of moderate-risk breast cancer-susceptibility genes, which found that half of patients with PVs in moderate-risk genes were diagnosed after age 50.²⁵ Moderate-risk genes are associated with a modestly increased breast cancer risk (OR 2–5), and increased risks for a varied spectrum of cancers.²⁶ Nonetheless, there can be a significant impact on management, such as the inclusion of contrast enhanced breast MRI for new primary breast cancer screening during survivorship. Moreover, cascade testing for family members can have a significant impact on cancer screening and prevention.⁷

Older women with sporadic breast cancer frequently have HR positive (60–80%) tumors.²⁷ In our cohort we found that older women with BC-related PVs less frequently had HR positive tumors when compared to those without BC-related PVs. *BRCA1*-associated tumors often do not express HR and human epidermal growth factor receptor 2 HER2, and approximately 70% are TNBC.²⁸ On the other hand, *BRCA2*-associated tumors are similar to sporadic tumors, with a quarter of cases being HR-negative and approximately 10% HER2-positive. In our study, the proportion of HR-positive tumors was 64%, which may be related with the higher proportion of *BRCA2* PVs among older adults. Our observation of clinical stage shift, with more advanced disease among younger women, may be related to the fact that older women are included in routine mammographic surveillance, though younger women would only be afforded screening if there were recognition of increased risk. Finally, caution must be exercised when a PV in *TP53* is identified in an older patient

as the frequency of clonal hematopoiesis rises with age, and we recently demonstrated somatic interference confounding clinical diagnoses in 23% of TP53 + cases from MGPT at a major commercial genetic testing vendor ^{24,29,30}.

Limitations that should be considered when interpreting our results include the modest sample size of older women compared to younger women; however, this still represents one of the largest studies of older women receiving genetic testing, with comprehensive clinical characteristics and family history data. There may be some bias in that this was a cohort of women referred for genetic counseling and testing. However, predictors of PV prevalence such as multiple primary cancers and ancestry were comparable between the younger and older breast cancer onset groups. Not surprisingly, family history of cancer was more frequent in the older group as that would have been a guideline criterion for genetic testing; it also might reflect the differences in the population and relatives' ages, such that the accumulated family cancer burden becomes more apparent. Though the study benefits from a long period of accrual and observation for the cohort, the breadth of genes included in the testing varied, generally increasing over time. However, this would only cause us to underestimate the burden of moderate risk gene PVs among the participants.

To better understand the role of genetic testing among older adults with breast cancer, future studies should assess the impact of risk reduction strategies in this population, taking into account life expectancy, comorbidities, patient preferences, quality of life, and competing risks.

CONCLUSION

This is the first study comparing breast cancer-associated PVs between older and younger female breast cancer onset. Overall, this study demonstrates that clinically actionable breast cancer related PVs in older breast cancer onset are frequent, and provides important evidence to support genetic testing for older women with BC, and that they should not be excluded based on chronological age alone.

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REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC CancerBase 2012; <http://globocan.iarc.fr>. Accessed 05/08/18, 2018.
2. American Cancer Society. Breast Cancer Facts & Figures 2017–2018 2018; <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf>. Accessed 05/08/18, 2018.
3. World Health Organization. Global Health and Aging 2011; <https://www.nia.nih.gov/research/dbsr/global-aging>. Accessed 05/08/18, 2018.
4. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol* 2009;27(17):2758–2765. [PubMed: 19403886]
5. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. *J Clin Oncol* 2018;36(22):2326–2347. [PubMed: 29782209]
6. Blackwood MA, Weber BL. BRCA1 and BRCA2: From molecular genetics to clinical medicine. *J Clin Oncol* 1998;16:1969–1977. [PubMed: 9586917]
7. NCCN. NCCN clinical practice guidelines in oncology V.1.2018: Genetic/Familial High-Risk Assessment: Breast and Ovarian. NCCN Clinical Practice Guidelines 2018;12018.
8. Rosenberg SM, Partridge AH. Management of breast cancer in very young women. *Breast* 2015;24 Suppl 2:S154–158. [PubMed: 26255745]
9. Slavin TP, Maxwell KN, Lilyquist J, et al. The contribution of pathogenic variants in breast cancer susceptibility genes to familial breast cancer risk. *NPJ breast cancer* 2017;3:22. [PubMed: 28649662]
10. Weitzel JN, Lagos VI, Cullinane CA, et al. Limited family structure and BRCA gene mutation status in single cases of breast cancer. *JAMA-J Am Med Assoc* 2007;297(23):2587–2595.
11. Gonzalez-Angulo AM, Timms KM, Liu S, et al. Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. *Clin Cancer Res* 2011;17(5):1082–1089. [PubMed: 21233401]
12. Greenup R, Buchanan A, Lorizio W, et al. Prevalence of BRCA mutations among women with triple-negative breast cancer (TNBC) in a genetic counseling cohort. *Ann Surg Oncol* 2013;20(10):3254–3258. [PubMed: 23975317]
13. Gonzalez KD, Noltner KA, Buzin CH, et al. Beyond Li Fraumeni Syndrome: Clinical characteristics of families with p53 germline mutations. *J Clin Oncol* 2009; 27(8):1250–1256. [PubMed: 19204208]
14. Hurria A, Mohile S, Gajra A, et al. Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer. *J Clin Oncol* 2016;34(20):2366–2371. [PubMed: 27185838]
15. Buys SS, Sandbach JF, Gammon A, et al. A study of over 35,000 women with breast cancer tested with a 25-gene panel of hereditary cancer genes. *Cancer* 2017;123(10):1721–1730. [PubMed: 28085182]
16. Walsh T, Casadei S, Coats KH, et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. *JAMA-J Am Med Assoc* 2006;295(12):1379–1388.
17. Tung N, Lin NU, Kidd J, et al. Frequency of Germline Mutations in 25 Cancer Susceptibility Genes in a Sequential Series of Patients With Breast Cancer. *J Clin Oncol* 2016;34(13):1460–1468. [PubMed: 26976419]
18. Slavin TP, Neuhausen SL, Nehoray B, et al. The spectrum of genetic variants in hereditary pancreatic cancer includes Fanconi anemia genes. *Fam Cancer* 2018;17(2):235–245. [PubMed: 28687971]
19. Weitzel JN, Clague J, Martir-Negron A, et al. Prevalence and type of BRCA mutations in Hispanics undergoing genetic cancer risk assessment in the southwestern United States: a report from the Clinical Cancer Genetics Community Research Network. *J Clin Oncol* 2013;31(2):210–216. [PubMed: 23233716]

20. Weitzel JN, Blazer KR, MacDonald DJ, Culver JO, Offit K. Genetics, genomics and cancer risk assessment: state of the art and future directions in the era of personalized medicine. *CA Cancer J Clin* 2011;61(5):327–359. [PubMed: 21858794]
21. Hall MJ, Reid JE, Burbidge LA, et al. BRCA1 and BRCA2 mutations in women of different ethnicities undergoing testing for hereditary breast-ovarian cancer. *Cancer* 2009;115(10):2222–2233. [PubMed: 19241424]
22. Weitzel JN, Lagos V, Blazer KR, et al. Prevalence of *BRCA* mutations and founder effect in high-risk Hispanic families. *Cancer Epidemiology, Biomarkers & Prevention* 2005;14(7):1666–1671.
23. Slavin T, Niell-Swiler M, Solomon I, et al. Clinical application of multigene panels: challenges of next-generation counseling and cancer risk management. *Frontiers in Oncology* 2015;5.
24. Weitzel JN, Chao EC, Nehoray B, et al. Somatic TP53 variants frequently confound germ-line testing results. *Genetics in medicine: official journal of the American College of Medical Genetics* 2018;20(8):809–816. [PubMed: 29189820]
25. Gorringer H, Rosenthal E, Kidd J, Brown K, Manley S. Trends in age of breast cancer diagnosis for women with pathogenic variants in genes associated with increased breast cancer risk. Paper presented at: San Antonio Breast Cancer Symposium 2016; San Antonio.
26. Easton DF, Pharoah PDP, Antoniou AC, et al. Gene-Panel Sequencing and the Prediction of Breast-Cancer Risk. *New Engl J Med* 2015;372(23):2243–2257. [PubMed: 26014596]
27. Muss HB. Coming of age: breast cancer in seniors. *Oncologist* 2010;15 Suppl 5:57–65. [PubMed: 21138956]
28. Peshkin BN, Alabek ML, Isaacs C. BRCA½ mutations and triple negative breast cancers. *Breast disease* 2010;32(1–2):25–33. [PubMed: 21778580]
29. Steensma DP, Bejar R, Jaiswal S, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood* 2015;126(1):9–16. [PubMed: 25931582]
30. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *The New England journal of medicine* 2014;371(26):2488–2498. [PubMed: 25426837]

Figure 1. Population flow chart. Patients with breast cancer diagnosis were enrolled to the CCGCRN. Patients were divided in two groups according to their age at diagnosis and pathogenic variant carrier status was assessed.

Table 1.

Breast cancer associated germline pathogenic variants

	< 65 years* n=1,340 (%)	65 years* n= 33 (%)	p value
High breast cancer risk genes	1248 (93.1%)	27 (80%)	0.01
BRCA1	666 (49.7%)	10 (28.5%)	0.02
BRCA2	469 (35%)	14 (40%)	0.47
PALB2	68 (5.0%)	3 (8.5%)	0.25
TP53	36 (2.6%)	0	-
PTEN	9 (<1%)	0	-
Moderate breast cancer risk genes	98 (7.3%)	7 (20%)	0.01
CHEK2	65 (4.8%)	5 (14.2%)	0.02
ATM	27 (2%)	1 (2.8%)	0.50
NF	3 (<1%)	1 (2.8%)	0.09
NBN	3 (<1%)	0	-

The presented n is # of subjects

* 1 patient 65y had more than one BC related pathogenic variants and 5 patients <65 y.

Clinical characteristics of older and younger women with breast cancer according to their pathogenic variant carrier status

Table 2.

	Older Carriers n= 33 (%)	Older No-carriers n=555 (%)	Older (carriers vs non-carriers) p value	Younger carriers N=1340 (%)	Younger non-carriers n=8072 (%)	Younger (carriers vs non-carriers) p value	Carriers (older vs younger) p value
BC stage							
0-IIA	21 (87.5%)	252 (85.8%)	1.0	428 (58%)	2713 (63.5%)	<0.01	<0.01
IIB-IV	3 (12.5%)	41 (14.2%)		310 (42%)	1555 (36.4%)		
HR status							
ER and/or PR +	16 (64%)	335 (80%)	0.07	508 (54.3%)	4257 (74.7%)	<0.01	0.41
ER and PR neg	9 (46%)	82 (20%)		427 (45.6%)	1439 (25.2%)		
Second BC	5 (14.7%)	56 (10.1%)	0.79	257 (19.1%)	881 (10.9%)	<0.01	0.66
FDR BC/OC	27 (79.4%)	403 (72.7%)	0.54	730 (54.4%)	2519 (31.2%)	<0.01	<0.01
AJ ancestry	3 (8.8%)	50 (9%)	1.0	77 (5.7%)	343 (4.2%)	0.01	0.44

BC: breast cancer; ER: estrogen receptor; PR: progesterone receptor; neg: negative; FDR: first degree relatives; OC: ovarian cancer; AJ: Ashkenazi Jewish.

* Missing values were not included in the table.