Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

J Geriatr Oncol. Author manuscript; available in PMC 2022 June 01.

Published in final edited form as:

J Geriatr Oncol. 2021 June ; 12(5): 749–751. doi:10.1016/j.jgo.2020.11.008.

Breast cancer associated pathogenic variants among women 61 years and older with triple negative breast cancer

Yanin Chávarri-Guerra[1], **Catherine A. Marcum**[2], **Carolyn B. Hendricks**[3], **Deborah Wilbur**[4], **Terrence Cescon**[5], **Christopher Hake**[6], **Julio Abugattas**[7], **Yenni Rodriguez**[8], **Cynthia Villarreal-Garza**[9], **Kai Yang**[10], **Aleck Cervantes**[10], **Sharon Sand**[10], **Danielle Castillo**[10], **Joseph Herzog**[10], **Janet Mokhnatkin**[10], **Mina S. Sedrak**[11], **Enrique Soto-Perez-de-Celis**[12], **Jeffrey N. Weitzel**[11]

[1]Department of Hemato-Oncology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City; Mexico

[2]CHI Memorial Rees Skillern Cancer Risk and Survivorship Center, Chattanooga, United States

[3]Maryland Oncology Hematology, Bethesda, United States

[4]Oncology Associates at Hall Perrine Cancer Center, Cedar Rapids, United States

[5]Reading Hospital, West Reading, United States

[6]Waukesha Memorial Hospital-Pro Health Care Research Institute, Waukesha, WI, USA

[7]Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru

Corresponding author: Jeffrey N. Weitzel, City of Hope Comprehensive Cancer Center, 1500 E. Duarte Rd, Duarte, CA 91010, Phone +1 (626) 218-8472, Fax +1 (626) 218-5495, jnweitzel57@gmai.com.

Authors Contributions:

Chavarri-Guerra: design and conceptualization; data analysis and interpretation; writing (original draft); writing (review and editing).
Marcum: patient accrual, writing (review and editing).
Hendricks: patient accrual, writing (review and editing).
Wilbur: patient accrual, writing (review and editing).
Cescon: patient accrual, writing (review and editing).
Hake: patient accrual, writing (review and editing).
Abugattas: patient accrual, writing (review and editing).
Rodriguez: patient accrual, writing (review and editing).
Villarreal-Garza: patient accrual, writing (review and editing).
Yang: data curation and interpretation; writing (review and editing).
Cervantes: data interpretation; writing (review and editing).
Sand: data curation and interpretation; writing (review and editing).
Castillo: data interpretation; writing (review and editing).
Herzog: data interpretation; writing (review and editing).
Mokhnatkin: writing (review and editing)
Sedrak: data interpretation; writing (review and editing).
Soto-Perez-de Celis: data interpretation; writing (review and editing).
Weitzel: design and conceptualization; funding acquisition; patient accrual; data interpretation; writing (review and editing).

Conflict of Interest:

Chavarri-Guerra: research support from Roche.
Weitzel: Speakers bureau for AstraZeneca

Sponsors Role: None.

This study was presented as an oral abstract at the annual meeting of the International Society of Geriatric Oncology in 2018.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[8]Instituo de Cancerología, Medellín, Colombia

[9]Hospital Hellion Zambrano- TecSalud, Monterrey, Mexico

[10]Department of Medical Oncology, Division of Clinical Cancer Genomics, City of Hope Comprehensive Cancer Center, Duarte, CA, USA

[11]Department of Medical Oncology and Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA, USA

[12]Cancer Care in the Elderly Clinic. Department of Geriatrics, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City; Mexico

Abstract

Women with triple negative breast cancer (TNBC) have a high prevalence of *BRCA1* mutations, and current clinical guidelines recommend genetic testing for patients with TNBC aged ≤60 years. However, studies supporting this recommendation have included few older women with TNBC.

Methods: Genetic testing results from women aged >60 years with TNBC enrolled in the Clinical Cancer Genomics Community Research Network (CCGCRN) registry were included in this analysis. Prevalence of breast cancer-associated pathogenic variants (PVs) was compared across age groups.

Results: We identified 151 women with TNBC aged >60 years (median 65 years; SD 5.3). Of these, 130 (86%) underwent genetic testing, and a breast cancer--associated PV was identified in 16 (12.3%; 95% CI 7–19): *BRCA1* (n = 6), *BRCA2* (n=5), *PALB2* (n = 2), *ATM* (n = 1) and *RAD51C* (n=2). We found no differences in the proportion of patients with close blood relatives with breast (≤50 years) or ovarian cancer (any age) between PV carriers (37.5%) and non-carriers (34.2%) (p=0.79). Among PVś carriers, the proportion of older women with a *BRCA1* PV was lower when compared to younger women (37.5% vs 77.2%; p<0.01).

Conclusion: Breast cancer-associated PVs were found in an important proportion of women aged >60 years with TNBC undergoing genetic testing, including greater representation of *BRCA2*. These results suggest that older women with TNBC should be offered genetic testing, and that their exclusion based on chronologic age alone may not be appropriate.

Keywords

Triple negative breast cancer; germline variants; older women

Introduction

Breast cancer (BC) is the most common malignancy among women aged ≥65 years worldwide. In 2018, 591,791 new BC cases were diagnosed and 225, 662 deaths were reported in this age group, representing the second cause of cancer-related deaths after lung cancer. As the population ages, the number of patients with BC is also expected to increase by about 70% over the next twenty years [1]. Older women most commonly present with hormone receptor positive breast cancer. However, a substantial proportion are diagnosed with triple negative breast cancer (TNBC) (estrogen receptor negative, progesterone receptor

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

negative and HER2 negative), which is associated with a more aggressive behavior [2]. TNBC is often caused by BC-associated germline mutations [3,4], and its presence is recognized as a criterion for genetic cancer risk assessment (GCRA) according to international guidelines. However, those same guidelines recommend that only women aged 60 years or younger should be considered as candidates for genetic testing and GCRA[5].

The prevalence of pathogenic variants (PVs) in BC susceptibility genes varies depending on risk factors such as age at diagnosis, family history of breast and ovarian cancer, and BC subtype. While older age is usually considered as an exclusion criteria for genetic testing, some recent publications suggest that the prevalence of BC-associated PVs among older women with BC is larger than previously thought [6].

We aimed to characterize the germline mutation profile of women with TNBC aged >60 years at the time of BC diagnosis in the Clinical Cancer Genomics Community Research Network (CCGCRN), a large consortium of collaborating clinics across the United States and Latin America.

Materials and Methods

Women aged 61 years or older at the time of TNBC diagnosis who were enrolled in the CCGCRN between 1997 and 2020 were included in this analysis. The CCGCRN is a large research group of over 40 collaborating sites in the United States and Latin America that serves as a biospecimen repository that includes personal and family medical history. TNBC was defined by the lack of expression of estrogen receptors (< 1% of cells with nuclear positivity), progesterone receptors (<1% of cells with nuclear positivity), and human epidermal growth factor receptor 2 (HER2) by immunohistochemistry (0 or 1+), or lack of amplification by in situ hybridization in the case of HER2. All women received GCRA at cancer centers and community-based clinics from sites in the United States and Latin America. Genetic testing was performed utilizing various methods and depended on availability of specific gene tests in that era and each institution's practice. Informed consent was obtained from all participants, and the institutional ethics review boards at each institution approved the study protocol.

Sociodemographic characteristics, clinical variables, multigenerational pedigrees, and genetic testing results were obtained from the CCGCRN database. Pathogenic and suspected PVs in genes known to be associated with increased BC risk were tailed according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards; and variants of uncertain significance (VUS) were also recorded. The observed prevalence of specific BC-associated PVs among older patients with TNBC was compared to that of the entire CCGCRN TNBC cohort, without age stratification.

Data are presented as medians, means, or proportions, and 95% confidence interval (CI) was calculated. Comparisons between women with and without PVs were performed using Fisher's Exact Test. A two-sided p-value of <0.05 was considered as statistically significant.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Results

From January 1997 to June 2020, a total of 1610 women with TNBC were identified in the CCGCRN registry database, of which 151 were aged >60 years (median 65 y; range 61–87) at the time of BC diagnosis and 19.2% (95%CI 12.8–27) were ≥ 70y. One-hundred and thirty (86%) participants underwent genetic testing, including multigene panel testing in 82 (63.0%) and *BRCA* testing in 48 (36.9%) women. Forty-eight (36.9%) patients reported a first or second-degree relative with breast or ovarian cancer. (Table 1)

A BC-associated PV was identified in 16 (12.3%; 95% CI 7–19) older women, while 22 (16.9%; 95% CI 10.4–23.3) had a VUS. Among women 61–69 y 11.4% (95% CI 6–19.1) carried a PV, while in women ≥70 y 16% (95% CI 4–36) were carriers. BC-associated PVs were identified in the following genes: *BRCA1* (n = 6), *BRCA2* (n = 5), *PALB2* (n = 2), *ATM* (n = 1) and *RAD51C* (n = 2). The characteristics of patients with TNBC harboring PVs are shown in Table 2. We found no differences in the proportion of patients with close blood relatives with breast (≤50 years) or ovarian cancer (any age) between PV carriers (37.5%) and non-carriers (34.2%) (p = 0.79). Among 1374 women aged ≤60 y, 373 (27.1%; 95% CI 24.8–29.5) carried a PV. Frequency of specific gene PVś were included in Table 3. Older women (aged >60 years) harboring BC-associated PVs had a significantly lower proportion of *BRCA1* PVs compared to younger women (37.5% vs 77.2%; p< 0.01). In contrast, the proportion of *BRCA2* PVs (31.2% vs 15.5%; p = 0.09) and of non-*BRCA* PVs (31.2% vs 7.2%; p<0.01) was higher among older women.

Discussion

In this study, we report the frequency of PVs in BC susceptibility genes among women aged >60 years with TNBC. Overall, 12.3% (95% CI 7–19) of older women with TNBC carried a BC-associated germline PV, most of which were located in *BRCA* genes.

The frequency found in our series is similar to previous studies reporting the prevalence of PVs in TNBC (9.4–18.2%) [7]. One clinical laboratory cohort, for example, reported a frequency of 12% in a large number of patients with TNBC of all age groups, while a multicenter study reported a prevalence of 14.6% [4]. However, in contrast with our study, in which the median age at diagnosis was 65 years, most series included patients with a median age at diagnosis of around 50 years. The finding of a similar prevalence of PVs among an older population shows that older women with TNBC are also at risk of carrying germline PVs. *BRCA1* and *BRCA2* were the most frequent BC-associated PVs in our study, although the relative proportion was shifted toward *BRCA2* among older patients. Interestingly, although *BRCA2* PVs are known to cause later onset disease, they have traditionally been associated with hormone receptor positive disease rather than TNBC. In addition, previous reports have described that the occurrence of TNBC among BRCA1 carriers [8] decreases with age. Our results suggest that *BRCA2* may play a role in the development of TNBC at older ages and warrants further investigation.

In addition to *BRCA* mutations, we also found other PVs among older women; including *PALB2*, *RAD51C* and *ATM*. Previous studies have reported a frequency of non-*BRCA*

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

mutations among patients with TNBC of 4%, which is consistent with our results (3.8% PVs in non-*BRCA* genes). However, we found a higher proportion of non-*BRCA* PVs among older women, which might be explained by a decrease in the frequency of *BRCA1* PVs. Although *PALB2* and *RAD51C* are less well characterized as TNBC-associated genes, both have been found to be enriched among women with this disease [9]. On the other hand, *ATM* is commonly found in other BC subtypes, and we have previously described *ATM* PVs in 3% of women 65 years and older with BC.

The proportion of older women with TNBC that has been included in genetic studies is small, and the range of reported PVs is wide (5.4 to 11.4%) depending on the selection criteria used for genetic testing [7], and on the number of genes studied. Couch et al. found that, among women aged ≥60 years, the risk of harboring a PV ranged from 4.7% among those without a family history of breast or ovarian cancer to 14.3% for those with a family history of ovarian cancer [4]. On the other hand, a study that selected women with TNBC who reported not to have any relatives with breast or ovarian cancer found a mutation frequency of 6.9% in *BRCA* genes among women aged >60 years at the time of diagnosis[3].

Although NCCN guidelines recommend testing all patients with TNBC aged ≤60 years our results, as well as other reports, have consistently shown that older women with TNBC are at higher risk of carrying PVs, and that clinicians should consider them as candidates for GCRA and genetic testing. Moreover, older women who carry PVs might be candidates for risk reducing strategies, as well as cascade testing in family members, who might also benefit from preventive strategies. Additionally, finding PVs in women with BC might guide therapy selection, such as the integration of platinum-based chemotherapy or poly ADP ribose polymerase (PARP) inhibitors.

Our study has some limitations that should be considered when interpreting our results including the sample size of older women and wide confidence intervals. In addition, only 82 older patients had multigene panel testing. However, this would only cause an underestimation of the burden of non-*BRCA* PVs among participants.

Overall, this study found a 12% prevalence of PVs in BC-associated genes among women with TNBC aged 60 years and older, with a high proportion of *BRCA2* PVs. We believe our results support a change in clinical recommendations and in clinical practice, such that all women with TNBC should receive genetic testing regardless of their chronological age.

Acknowledgments

This research was supported in part by a grants from the Breast Cancer Research Foundation, and the Conquer Cancer Research Professorship in Breast Cancer Disparities (J. Weitzel), as well as National Institutes of Health grant RC4 CA 153828 (J. Weitzel), and a supplement, “Strengthening capacity to promote cancer risk assessment dissemination and implementation research and translation among underserved populations in the Americas” (Rosen/Weitzel), to award number P30CA33572. Some sequencing was performed in the functional Genomics Core, supported by P30CA033572. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health. We wish to thank the participants who enabled this research.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

References

1. Ferlay J, Ervik M, Lam F, et al.: Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer, Global Cancer Observatory, 2018
2. Howlader N, Altekruse SF, Li CI, et al. : US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 106, 2014
3. Shimelis H, LaDuca H, Hu C, et al. : Triple-Negative Breast Cancer Risk Genes Identified by Multigene Hereditary Cancer Panel Testing. JNCI: Journal of the National Cancer Institute 110:855–862, 2018 [PubMed: 30099541]
4. Couch FJ, Hart SN, Sharma P, et al. : Inherited Mutations in 17 Breast Cancer Susceptibility Genes Among a Large Triple-Negative Breast Cancer Cohort Unselected for Family History of Breast Cancer. Journal of Clinical Oncology, 2015
5. NCCN: NCCN Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2020-December4, 2019., NCCN Clinical Practice Guidelines, 2019
6. Chavarri-Guerra Y, Hendricks CB, Brown S, et al. : The Burden of Breast Cancer Predisposition Variants Across The Age Spectrum Among 10 000 Patients. Journal of the American Geriatrics Society 67:884–888, 2019 [PubMed: 31012959]
7. Hahnen E, Hauke J, Engel C, et al. : Germline Mutations in Triple-Negative Breast Cancer. Breast Care (Basel) 12:15–19, 2017 [PubMed: 28611536]
8. Mavaddat N, Barrowdale D, Andrulis IL, et al. : Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Cancer Epidemiology, Biomarkers & Prevention 21:134–47, 2012
9. 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 123:1721–1730, 2017 [PubMed: 28085182]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

Clinico-demographic characteristics

	N = 130 (%)	95% CI
Median age at TNBC (range)	65 (61–87)	
≥70 years	25 (19.2)	(12.8–27)
Second BC	12 (9.2)	(4.8–15.5)
Family history of cancer	48 (36.9)	(28.6–45.8)
FDR breast cancer	17 (13.0)	(7.8–20.1)
SDR breast cancer	20 (15.3)	(9.6–22.7)
FDR/SDR ovarian cancer	20 (15.3)	(9.6–22.7)

BC: breast cancer; CI: confidence interval; FDR: first degree relative; SDR: second degree relative; TNBC: triple negative breast cancer.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2

Breast cancer associated PVs and patients' characteristics

Gene	Nucleotide change	Age at diagnosis	Family history
ATM	c.1402_1403delAA	63	None
BRCA1	c.2463G>T	65	2 FDR w/OC
BRCA1	c.5123C>A	68	FDR and SDR w/OC
BRCA1	c.3756_3759del	74	None
BRCA1	c.68_69delAG	67	None
BRCA1	exon16-17del	78	2 SDR w/ BC
BRCA1	c.2498T>A	61	SDR w/ BC
BRCA2	c.5073dupA	63	FDR w/OC
BRCA2	c.3058A>T	65	None
BRCA2	c.6352C>T	61	None
BRCA2	c.5946delT	73	None
BRCA2	c.8837T>T	68	None
PALB2	c.509_510delGA	67	None
PALB2	c.3113G>A	66	SDR w/OC
RAD51C	c.709C>T	66	None
RAD51C	c.404+2T>C	70	None

FDR: first degree relative; SDR: second degree relative; BC: Breast cancer; OC: ovarian cancer.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 3.

Comparison of BC-associated PVs prevalence among older and younger women with TNBC

Gene	Total n= 389 (%)	≤60 y n=373 (%)	>60 y n = 16 (%)	*P (≤ 60 vs > 60 y)*
BRCA1	**294 (75.5)**	**288 (77.2)**	**6 (37.5)**	**< 0.01**
BRCA2	**63 (16.1)**	**58 (15.5)**	**5 (31.2)**	**0.09**
Non-*BRCA*:	**32 (8.2)**	**27 (7.2)**	**5 (31.2)**	**< 0.01**
ATM	1 (0.2)	0	1 (6.25)	
BARD1	2 (0.5)	2 (0.5)	0	
BRIP1	2 (0.5)	2 (0.5)	0	
CHEK2	3 (0.7)	3 (0.8)	0	
PALB2	13 (3.3)	11 (2.9)	2 (12.5)	
PTEN	1 (0.2)	1 (0.2)	0	
RAD50	1 (0.2)	1 (0.2)	0	
RAD51C	4 (1.0)	3 (0.8)	2 (12.5)	
RAD51D	3 (0.7)	3 (0.8)	0	
TP53	1 (0.2)	1 (0.2)	0	