Prospective Evaluation of Universal BRCA Testing for Women With Triple-Negative Breast Cancer

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Abstract

Background: Limited published literature exists on women with triple-negative breast cancer (TNBC) diagnosed over the age of 60 years with breast cancer gene (BRCA) pathogenic variants. Our study determined whether the rate of BRCA pathogenic variants in a prospective cohort of TNBC patients outside the definition of current clinical genetic testing (GT) guidelines warrants a change in recommendations. Methods: A prospective study of 395 women with TNBC underwent genetic counseling and 380 (96.2%) underwent clinical BRCA GT regardless of age of diagnosis beginning January 2014 to October 2015 at The University of Texas MD Anderson Cancer Center, Houston. TNBC patients older than 60 years who did not meet clinical GT guidelines had comprehensive sequencing and large rearrangement GT as part of the research protocol. Results: Fifty-one of 380 (13.4%) women with TNBC who underwent clinical BRCA GT were BRCA positive. Of the 86 patients diagnosed at age over 60 years and underwent GT, only two (2.3%) were positive for BRCA. These two patients would have met clinical testing criteria due to family or ancestral history. Conclusions: Our study does not support universal BRCA testing for TNBC patients diagnosed older than 60 years as their only risk factor for a BRCA pathogenic variant. Both of the positive BRCA patients older than 60 years identified would have met current National Comprehensive Cancer Network criteria for testing. Therefore, our study demonstrates that the National Comprehensive Cancer Network guidelines provide sufficient criteria for identifying BRCA pathogenic variants in women with TNBC at 60 years or younger.

Triple-negative breast cancer (TNBC) is a heterogeneous subtype of breast cancer identified as estrogen receptor (ER) negative, progesterone receptor (PR) negative, and human epidermal growth factor receptor 2 (HER2/neu) negative. These three receptors are absent in approximately 15–20% of breast cancer case patients in the United States (1,2). TNBC’s clinical features include an increased mortality rate during the first 5 years and risk of recurrence occurring between 1 and 3 years (3).

Pathogenic variants (commonly referred to as “germline pathogenic variants”) in breast cancer genes (BRCA1) or BRCA2 statistically significantly increase the overall lifetime risk for breast and ovarian cancers in women (4,5). Women with TNBC have an 11–31% likelihood of possessing a BRCA pathogenic variant (6–11). The National Comprehensive Cancer Network (NCCN) published clinical testing guidelines that recommended individuals with TNBC age 60 years or younger undergo BRCA genetic testing (GT) (12). Clinical criteria for testing individuals with TNBC also include those with a family history (FH) per NCCN clinical testing guidelines (12). BRCA pathogenic variants in TNBC patients have implications for early cancer detection and cancer prevention in at-risk blood relatives (13–16). Our previous prediction models have shown that testing all TNBC patients younger than 50 years may reduce the risk of new breast cancers by 23% and ovarian cancers by 41% (11). Furthermore, a recent study has shown that BRCA pathogenic variants in affected patients can have important treatment implications, hence stressing the importance of identifying patients with BRCA pathogenic variants (16).

Although NCCN recommends BRCA GT for patients with TNBC younger than 60 years, some studies suggest that increasing the recommended age of testing to older than 60 years may identify more TNBC patients with BRCA pathogenic variants (6).
Furthermore, recent promising results of oral polyadenosine diphosphate-ribose polymerase (PARP) inhibitors for metastatic breast cancer with BRCA pathogenic variants may tempt healthcare providers to test all TNBC patients for BRCA (17–19). Therefore, our aim in this study was to determine whether the rate of BRCA pathogenic variants in a prospective cohort of TNBC patients outside the definition of current clinical GT guidelines warrants a change in recommendations.

Methods

Cohort Identification

Consecutive patients with TNBC underwent genetic counseling (GC) regardless of age of diagnosis between January 2014 and October 2015. Written informed consent was obtained, and this prospective study was approved by The University of Texas MD Anderson Cancer Center’s (UTMDACC) institutional review board. All patients were referred by UTMDACC physicians or outside physicians and evaluated by the Clinical Cancer Genetics Program. They were offered GC and upon completion of the session, if agreed, were consented to the study and GT for the BRCA1 and BRCA2 genes. TNBC patients age 60 years or younger underwent clinical GT (12). Patients with prior BRCA comprehensive sequencing testing underwent testing for BRCA large rearrangement. TNBC patients with personal and/or FH who met clinical BRCA testing criteria may have undergone clinical GT for additional genes other than BRCA as clinically indicated after pedigree review. TNBC patients over the age of 60 years without an FH according to NCCN guidelines, who did not meet clinical GT criteria, underwent research comprehensive sequencing and large rearrangement GT for BRCA1 and BRCA2 (Integrated BRACAnalysis) through Myriad Genetic Laboratories, Inc. as part of an institutional review board-approved human patients research protocol with written consent among participants. FH was defined by February 2015 NCCN guidelines (12).

TNBC Pathology

TNBC was defined as ER and PR 0–9% hormone receptor low-positive tumor and HER2/neu gene 0, 1+, or 2+ with no amplification via FISH of a ratio of less than 2.0 (20). ER and PR 0–9% inclusion criteria were used based on a Sanford et al. (20) publication and have become standard in our practice. Patients with pathology records from an outside institution had their pathology reviewed by breast pathologists at UTMDACC. If discrepancies occurred between the outside pathology report and the institution’s pathology review, our institution’s pathology was used to determine the patient’s eligibility for the study. If both HER2/neu immunohistochemistry and fluorescence in situ hybridization were available, fluorescence in situ hybridization was used as the preferred HER2/neu evaluation.

Statistical Methods

The objective of the study was to determine if there is an increased identification of high-risk hereditary breast cancer patients through implementation of universal BRCA1 and BRCA2 GT of all women with TNBC. Data were summarized with descriptive statistics (ie, means, SDs, frequencies, and percentages). The Fisher test was used to analyze the age group and BRCA pathogenic variant status considering one table cell had an expected cell count of less than five. P less than .05 indicated statistically significant difference. IBM SPSS Statistics Version 22 (SPSS, Inc, Armonk, NY) was used to analyze the data. All tests were two-sided.

Results

All TNBC patients were referred for GC and GT at UTMDACC. A total of 395 of 424 TNBC UTMDACC (93.4%) patients were included in this study. All 395 female patients were eligible based on pathology report review confirming TNBC. Our study targeted stage I–III TNBC patients during enrollment, in which 360 (91.1%) of 395 were stage I–II, and 35 of 395 ended up having stage IV TNBC after their complete work-up. All 395 TNBC female patients underwent GC. Of those, 380 underwent GT. From TNBC diagnosis to GT, 278 of 380 (73.2%) had GT within 1 year. A summary of the length of time from TNBC diagnosis to GT is found in Table 1. Patient demographics are summarized in Table 2 and Figure 1. The overall median age of TNBC diagnosis was 52.0 years (range, 25.0–84.0 years), the median age of TNBC diagnosis for patients diagnosed age 60 years or younger was 48.0 years (range, 25.0–60.0 years), and the median age of TNBC diagnosis for patients diagnosed older than 60 years was 65.0 years (range, 61.0–84.0 years). A total 206 (52.2%) of the study population were white, 85 (21.5%) were black, 67 (17.0%) were Hispanic, and 26 (6.6%) were Asian. Thirteen (3.3%) reported Ashkenazi Jewish (AJ) ancestry, and 11 (2.8%) did not have any ancestry information available.

A total 380 (96.2%) of 395 eligible patients underwent BRCA GT. Fifty-one of 380 (13.4%) were identified as having a BRCA pathogenic variant, 45 of 380 (11.8%) had a BRCA1 pathogenic variant, and six patients (1.6%) had a BRCA2 pathogenic variant. Additional study population demographics (ie, race, ER, PR, and HER2/neu) are listed in Table 2. Fifteen of 395 (3.8%) were not tested; 10 of 395 (2.5%) patients decided not to pursue BRCA testing, indicating they would like more time to consider GT, and five of 395 (1.3%) did not give a specific reason for declining. Eight of 395 (2.0%) met clinical testing criteria based solely on the age of diagnosis, four of 395 (1.0%) met clinical testing criteria based solely on FH, and one of 395 (0.3%) met clinical testing criteria based on age of diagnosis and FH.

The overall median age of BRCA positive patients was 42.0 years (range, 25.0–64.0 years). The rate of BRCA pathogenic variants comparing groups of patients age 60 years or younger with those older than 60 years is summarized in Table 3. Out of 380 tested patients, 294 (77.4%) were in the group younger than 60 years. Among these, 49 (16.7%) were BRCA positive and 237 (80.6%) were BRCA negative. Of 380 tested patients, 86 (22.6%) were in the group older than 60 years. Among these, two (2.3%) were BRCA positive and 80 (93.0%) were BRCA negative. Using the Fisher test, there was a statistically significant difference between the rate of BRCA pathogenic variants in those 60 years and younger and those older than 60 years (P = .001). Two of 86 (2.3%) patients older than 60 years who were BRCA positive would have met current NCCN guidelines for GT based on family or ancestral history. Patient A was diagnosed with TNBC at 64 years; however, there was a known BRCA1 pathogenic variant, 358del3insTT, previously identified in the family. Patient B was diagnosed with TNBC at 62 years and reported bilinear AJ ancestry. Patient B tested positive for an AJ founder pathogenic variant BRCA1, c.68_69delAG (p.Glu23Valfs).

In addition to age of diagnosis, we further analyzed BRCA pathogenic variant status based solely on FH. We identified patients with an FH of breast and/or ovarian (BOV) cancer. Of
390 patients included in the FH analyses, 159 (40.8%) had an FH of BOV. A total of 155 of 390 (39.7%) patients with an FH of BOV underwent GT. Of those 155 with an FH of BOV who underwent GT, 35 (22.6%) patients were BRCA positive. The details of BRCA pathogenic variant prevalence based on FH for additional cancer relationships (breast, ovarian, pancreatic, and prostate) are listed in Table 4. Patients who were adopted or did not have any FH available were not included in this portion of the analyses.

Discussion

Our study does not support universal BRCA testing for TNBC patients diagnosed older than 60 years as their sole risk factor for a BRCA pathogenic variant. Both of the positive BRCA patients older than 60 years old identified would have met current NCCN criteria for testing based on their FH or ancestry. Of note, the GC referral guidelines at our institution include a holistic view of the patient’s personal and FH of cancer. The guidelines serve to refer appropriate patients for GC, in which they would receive a detailed risk assessment to determine if GT for BRCA is warranted. This policy increases the likelihood that patients who are appropriate for GC and/or GT are captured during their care at our institution. Individuals who order GT are expected to utilize clinical judgement and professional guidelines to determine who may benefit from GT and what specific testing is beneficial for that individual. Our study demonstrates that NCCN guidelines provide sufficient criteria for identifying BRCA pathogenic variants in women with TNBC at age 60 years or younger.

With the implementation of universal BRCA testing of TNBC patients, our study found 51 of 380 (13.4%) total BRCA deleterious pathogenic variants regardless of age of diagnosis. Hartman et al. (6) performed a retrospective study identifying a 10.6% prevalence rate of BRCA pathogenic variants, regardless of age of diagnosis, in an unselected community oncology network patient population of TNBC. Their testing cohort categorized individuals with TNBC based on their age of diagnosis of younger than 50 years and 50 years or older (6). They did not report specifically on individuals diagnosed with TNBC at age 60 years or older (6). Sharma et al. (8) prospectively studied Kansas City academic and community practices, which exhibited a 15.5% prevalence rate of BRCA pathogenic variants among patients, including all ages of TNBC diagnosis. Three of 32 positive BRCA1/2 individuals in their cohort were over the age of 60 years at time of diagnosis (8). All three individuals would have met NCCN testing guidelines based on their additional personal and/or FH (8). Greenup et al. (9) performed a retrospective study identifying a 30.9% BRCA positive prevalence for a TNBC GC cohort. In their BRCA positive patient population, five of 139 positive BRCA1/2 patients were 60 years or older when they were diagnosed with cancer (9). It is unknown whether these five patients would have met clinical testing criteria based on their FH or ancestry (9). As noted in their report, their high BRCA positive prevalence of 30.9% may be an overestimate in an unselected TNBC group due to the selection of their own cohort of patients referred to GC based on FH and early onset of diagnosis (9). Couch et al. (10) compiled 12 different TNBC studies and identified 11.2% of TNBC patients with BRCA1 (8.5%) and BRCA2 (2.7%) pathogenic variants. Twelve of 204 BRCA1 or BRCA2 positive TNBC patients were older than 60 years (10). From those older than 60 years and without an FH of cancer, only 1.4% had a BRCA pathogenic variant (10). Their study supported the NCCN guidelines that testing for BRCA in TNBC women should only be implemented before 60 years of age in the absence of FH.

Table 1. Length of time from TNBC diagnosis to BRCA GT (N = 380)*

| Length of time, y | No. (%) |
|------------------|---------|
| 0–1              | 278 (73.2) |
| <2               | 20 (5.3) |
| 3–5              | 29 (7.6) |
| 6–10             | 21 (5.5) |
| >11              | 32 (8.4) |

*GT = genetic testing; TNBC = triple-negative breast cancer.

Figure 1. Universal BRCA testing for women with TNBC study population flow chart. GT = genetic testing; + = positive; − = negative; TNBC = triple-negative breast cancer; VUS = variant of uncertain significance.
The results of our study did not indicate an increase in the identification of BRCA positive TNBC women outside of the current NCCN guidelines. Of 86 patients older than 60 years who underwent GT, only two (2.3%) were BRCA positive. Both individuals would have met NCCN clinical testing criteria due to FH or ancestral history. Studies have found 3–13% positive BRCA pathogenic variants in those 60 years or older (6,8–10). As seen in Table 5, our smaller percentage of 2.3% in contrast to previous studies could be due to our institution’s earlier identification of TNBC in patients; thus, referral for GC and diagnosis of BRCA positivity occurs earlier. Implementing universal testing of all women with TNBC, regardless of age, would require greater resources, specifically an additional consultation for GC for each patient. In the case of a low-risk patient, they may incur additional costs for GC and/or GT when there are no substantive recommendations. Based on these study results and the NCCN criteria, GC and GT for patients with TNBC are likely to be recommended when deemed appropriate for the patient (based on age of onset and/or FH). Our findings are comparable with previous studies in the literature showing that BRCA testing for TNBC older than 60 years is not indicated unless the patients meet other clinical testing criteria. The outlined NCCN criteria provide the ability to capture individuals with BRCA pathogenic variants based on several personal and FH characteristics. This study emphasizes that utilizing FH and ancestry are important indicators for BRCA positivity in individuals, specifically TNBC women older than 60 years. Although detecting BRCA pathogenic variants affects an individual’s management recommendations and possible targeted therapy options, the means by which individuals are identified as appropriate candidates for BRCA GT should follow the current NCCN guidelines.

Patients without an FH for BOV cancer and PANPRO cancer had a BRCA pathogenic variant prevalence of 6.1% regardless of age of diagnosis. Patients with an FH of BOV cancer had a prevalence rate of a BRCA pathogenic variant at 22.6%. Our study further supports the higher prevalence rate of a BRCA pathogenic variant in families with an FH of BOV (6,8). Additionally, our study evaluates the likelihood of identifying a BRCA pathogenic variant in individuals based on the NCCN testing criteria for the BRCA1/2 genes only. As the knowledge and interest in GT increases in both providers and patients alike, many individuals who elect to undergo GT are more likely to receive testing of many genes (ie, panel test) without considering the implications of other genes. BRCA pathogenic variants have been well established to be associated with TNBC; however, many genes on large panel tests do not have an association with TNBC. This type of testing is particularly unnecessary if TNBC is the only basis for testing. GT for multiple genes may benefit some patients when coupled with clinical judgement. When GT is not clinically warranted, uncertainty may increase, as is the case with variants of uncertain significance (VUS). The VUS rate increases as more genes are added to the analysis. If a patient is recommended to undergo GT based on a history of TNBC older than 60 years with no additional personal or FH, they are susceptible to large hereditary cancer panels with genes not associated with their diagnosis. In turn, they have a higher likelihood of identifying a VUS and may be mismanaged based on

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### Table 2. Universal BRCA testing for women with TNBC study population demographics

| Category          | ≤60 y | >60 y | Total |
|-------------------|-------|-------|-------|
| No. in age group  | 302   | 95    | 397   |
| Underwent GT      | 294   | 86    |       |
| BRCA status       |       |       |       |
| Positive          | 49    | 2     | 0.01  |
| Negative          | 237   | 80    |       |
| VUS               | 8     | 4     |       |

*Fisher test, two-sided. GT = genetic testing; TNBC = triple-negative breast cancer; VUS = variants of uncertain significance.

### Table 3. Rate of BRCA pathogenic variants in TNBC patients between age groups (N = 395)

| Category          | ≤60 y, No. | >60 y, No. | P*  |
|-------------------|------------|------------|-----|
| No. in age group  | 302        | 93         |     |
| Underwent GT      | 294        | 86         |     |
| BRCA status       |            |            |     |
| Positive          | 49         | 2          | .001|
| Negative          | 237        | 80         |     |
| VUS               | 8          | 4          |     |

*Fisher test, two-sided. GT = genetic testing; TNBC = triple-negative breast cancer; VUS = variants of uncertain significance.
incorrect interpretation of a VUS or limited information about other genes that may be present on the panel test. It is important to emphasize that BRCA testing criteria are not created to determine the likelihood of testing positive for a non-BRCA gene.

Without the presence of cellular receptors for targeted breast cancer treatment, TNBC therapy is more limited to chemotherapy, surgery, and radiation therapy. First-line treatment for TNBC has been a combination of anthracyclines and taxanes (21). Tumors resistant to anthracyclines or taxanes have created limited chemotherapeutic options for TNBC patients. Recently, targeted therapies such as PARP inhibitors have been found useful specifically for pathogenic BRCA variants (22,23). TNBC patients who previously failed chemotherapy or who have a rapidly metastatic disease were found to have a longer progression-free survival compared with non-BRCA mutated patients when treated with PARP inhibitors (24–26). Ongoing trials are studying the effects of iniparib, olaparib, and veliparib (24–26). Due to the aggressiveness of TNBC tumors, health-care providers might be tempted to recommend BRCA testing to all TNBC patients for possible treatment with PARPs; however, our study demonstrates standard NCCN guidelines are sufficient to diagnose BRCA pathogenic variants.

A limitation of our study is the small sample size due to the fact the study population was obtained from a GC cohort. Only those patients referred for GC underwent GT. There is a possibility that other TNBC patients were missed because they were not referred; however, based on the historical data of our institution, only fewer than 10% were not referred.

In conclusion, BRCA testing of patients with TNBC older than 60 years, based on age alone, does not yield clinically significant results. To our knowledge, our study provides an addition to the important data found in TNBC women older than 60 years of age. With recent promising data using targeted therapies (PARP inhibitors) in BRCA positive breast cancer, health-care providers might be tempted to recommend testing to all TNBC patients (17–19); however, the results of this study should be taken into consideration and standard NCCN testing guidelines should be followed.

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| Table 4. BRCA pathogenic variant prevalence on TNBC women based on FH (n = 390) |
|---------------------------------------------------------------|
| **Family history** |
| **BOV** |
| **Category** | None | With and without PANPRO | With PANPRO | Without PANPRO | PANPRO without BOV |
|--------------|-------|-------------------------|-------------|----------------|-------------------|
| **Total**    | 208 (53.3) | 159 (40.8) | 18 (4.6) | 141 (36.2) | 23 (5.9) |
| Age of Dx, y |       |           |           |               |                  |
| Mean (SD)    | 51.1 (11.52) | 51.7 (11.2) | 52.6 (9.17) | 51.6 (11.50) | 52.3 (11.13) |
| Median       | 51.0 | 52.0 | 54.5 | 52.0 | 55.0 |
| Range        | 25.0–81.0 | 29.0–84.0 | 32.0–71.0 | 29.0–84.0 | 26.0–80.0 |
| Underwent GT |       |           |           |               |                  |
| Yes          | 197 (50.5) | 155 (39.7) | 18 (4.6) | 137 (35.1) | 23 (5.9) |
| <60          | 151 (38.7) | 124 (31.8) | 15 (3.8) | 109 (27.9) | 15 (3.8) |
| >60          | 46 (11.8) | 31 (7.9) | 3 (0.8) | 28 (7.2) | 8 (2.1) |
| BRCA status  |       |           |           |               |                  |
| Positive     | 12 (6.1) | 35 (22.6) | 1 (5.6) | 34 (24.8) | 3 (13.0) |
| BRCA1        | 10 (5.1) | 32 (20.6) | 0 (0.0) | 32 (23.4) | 2 (8.7) |
| BRCA2        | 2 (1.0) | 3 (1.9) | 1 (5.6) | 2 (1.5) | 1 (4.3) |
| <60          | 12 (6.1) | 33 (21.3) | 1 (5.6) | 32 (23.4) | 3 (13.0) |
| >60          | 0 (0.0) | 2 (1.3) | 0 (0.0) | 2 (1.5) | 0 (0.0) |
| Negative     | 176 (44.9) | 117 (75.5) | 17 (94.4) | 100 (73.0) | 20 (87.0) |
| ≤60          | 133 (67.5) | 89 (57.4) | 14 (77.8) | 75 (54.7) | 12 (52.2) |
| >60          | 43 (21.8) | 28 (18.1) | 3 (16.7) | 25 (18.2) | 8 (34.8) |

*TNBC patients who were adopted or did not have any FH available were not included in this analysis. BOV = breast and/or ovarian cancer; Dx = diagnosis; FH = family history; GT = genetic testing; PANPRO = pancreatic and/or prostate cancer; TNBC = triple-negative breast cancer.

| Table 5. Summary of BRCA pathogenic variant prevalence in women with TNBC* |
|-------------------------------------------------------------|
| Study                                                      |
| Total BRCA pathogenic variant No. (%)                      |
| Age group, y (No.)                                         |
| >60 y BRCA pathogenic variant No. (%)                     |
| Our study (n = 380)                                        | 51 (13.4) | >60 (86) | 2 (2.3) |
| Hartman et al. 2012 (6) (N = 199)                          | 21 (10.6) | >60 (45) | 2 (4.4) |
| Greenup et al. 2013 (9) (n = 450)                          | 139 (30.9) | >60 (38) | 5 (13.2) |
| Sharma et al. 2014 (8) (N = 207)                           | 32 (15.5) | >60 (61) | 3 (4.9) |
| Couch et al. 2015 (10) (N = 1824)                          | 204 (11.2) | >60 (388) | 12 (3.1) |

*TNBC = triple-negative breast cancer.
Notes
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