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EPIDEMIOLOGY

Outcome of triple negative breast cancer: comparison of sporadic and BRCA1-associated cancers

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Abstract The majority of breast cancers developing in *BRCA1* mutation carriers are triple negative breast cancers (TNBC), an aggressive subtype that accounts for 15–20 % of sporadic breast cancer. We compare the clinical outcome and sites of relapse of TNBC in *BRCA1* mutation carriers and non-carriers who received adjuvant chemotherapy. Women with stage I–III TNBC who had *BRCA1* testing within 36 months of diagnosis and received adjuvant chemotherapy were identified from clinical databases at two academic institutions. Sites of relapse, freedom from distant metastasis (FFDM), and breast cancer-specific survival (BCSS) were determined. *RCA1* carriers ($n = 89$) were significantly younger at diagnosis ($P < 0.0001$) than non-carriers ($n = 175$). FFDM at 5 years was 80.5 % for carriers and 76.9 % for non-carriers; with median follow-up of 55 months, hazard ratio (HR) was 0.90, $P = 0.71$. Sites of recurrence, including brain, did not differ significantly. BCSS at 5 years was 88.1 % for carriers and 81.4 % for non-carriers; HR 0.60; $P = 0.15$ at 55 months follow-up. *BRCA1* carriers who underwent oophorectomy had a significantly lower rate of death from TNBC, with an adjusted HR of 0.30 (95 % CI 0.10–0.94). Adjusting for age, oophorectomy, and prophylactic mastectomy, *BRCA1* mutation status was not an independent predictor of survival (HR 2.1; $P = 0.13$). *BRCA1* mutation carriers with TNBC had similar survival rates and sites of recurrence to non-carriers after treatment with conventional chemotherapy. Carriers who underwent oophorectomy had a significantly lower rate of breast cancer-related death; this finding should be studied further in all women with TNBC.

Keywords Triple negative breast cancer · *BRCA1* · Oophorectomy · Brain metastasis · Sites of recurrence

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Introduction

Triple negative breast cancer (TNBC), defined as tumors lacking expression of estrogen receptor (ER), progresterone receptor (PR), and epidermal growth factor receptor 2 (HER2), accounts for approximately 15–20 % of all breast cancer [1]. It is more common in young and African-American women as well as those who inherit a *BRCA1* mutation. Approximately 70 % of breast cancers that develop in women with germline *BRCA1* mutations are TNBC and among unselected women with TNBC, 10–20 % have a germline *BRCA1* mutation [2–4]. Compared to other breast cancer subtypes, TNBC is associated more often with visceral metastases to the brain and lung and less often to bone, and is associated with worse breast cancer and overall survival [1, 5, 6].

We previously reported no difference in breast cancer-specific survival (BCSS) among 117 women with TNBC according to *BRCA1* status but noted that *BRCA1* mutation

carriers (*BRCA1* carriers) had a higher frequency of brain metastases (58 vs. 24 %; $P = 0.06$) [7]. The goal of this study is to extend the investigation of this initial cohort in order to further evaluate both long-term outcomes and patterns of TNBC recurrence, including frequency of brain metastases, in patients segregated by *BRCA1* status. Information regarding the prognosis of a possible future breast cancer is extremely important for *BRCA1* carriers who must decide between breast cancer surveillance and prophylactic surgery.

Materials and methods

This is a retrospective cohort study of women diagnosed with a first-invasive TNBC, Stage I–III between 1 January 1996 and 31 December 2004. Women must have received adjuvant or neoadjuvant chemotherapy and undergone *BRCA1* testing. BRCA2 mutation carriers were excluded. ER, PR, and HER2 status were assessed as part of the routine clinical evaluation and abstracted from institutional pathology reports. Only women who had genetic testing within 36 months of breast cancer diagnosis were included in order to limit the potential survivorship bias of delayed genetic testing. The initial 117 cases (46 *BRCA1*-carriers and 71 sporadic TNBC) identified through the Beth Israel Deaconess Medical Center (BIDMC) and Dana-Farber Cancer Institute (DFCI) were previously reported [7]. For the current analysis, an additional 185 cases of TNBC were identified through the cancer genetic testing programs at BIDMC and DFCI. Seventy-eight women were excluded for the following reasons: more than 36 months from diagnosis to genetic testing ($n = 64$), no follow-up ($n = 8$), stage IV disease at testing ($n = 3$), no adjuvant chemotherapy ($n = 2$), and diagnosis before 1996 ($n = 1$).

Clinical data were abstracted from the medical record, including review of pathology reports, operative notes, treatment data, and clinic visits with the approval of the Dana Farber/Harvard Cancer Center Institutional Review Board.

The majority (90 %) of chemotherapy regimens contained an anthracycline backbone, most commonly doxorubicin and cyclophosphamide (AC), doxorubicin, cyclophosphamide, 5-fluoruracil (CAF) or doxorubicin, cyclophosphamide followed by paclitaxel (AC + T). Docetaxel and cyclophosphamide (TC) was used in 13 subjects, and cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in 11 subjects.

Surgery was mastectomy in 120 patients (45 %) and partial mastectomy in 144 (55 %). One hundred eighty-seven patients (71 %) received adjuvant radiation.

Routine follow-up visits after the completion of therapy included an interview history and physical examination, and were conducted every 3 or 6 months for 3 years, and thereafter every 6 months per institutional practice. Surveillance imaging was performed at the discretion of the treating physician. Computed tomography of the chest, abdomen and pelvis, magnetic resonance imaging of the brain, and radionuclide bone scan were used to investigate potential sites of metastases. Recurrent disease was classified as local–regional, distant, or both. Local–regional recurrence was defined as recurrent disease in the ipsilateral breast, draining lymph nodes (axilla, supraclavicular, or internal mammary chain), or chest wall. The first and subsequent sites of distant metastatic involvement were documented after restaging studies were performed. The diagnosis of a second cancer was also recorded.

All statistical analyses were conducted with SAS 9.3 (SAS Institute, Cary, NC, USA) and Stata 12 (StataCorp, College Station, TX, USA). Descriptive data are presented as mean ± standard deviation, median [interquartile range (IQR)] or proportion. Continuous data were compared using a *t* test or Wilcoxon rank sum test, and categorical data were compared with the χ^2 or Fisher's exact test. All tests were two-sided and $P < 0.05$ was considered statistically significant. We used the Kaplan–Meier estimator to compute the survival function and compared survival curves using the log-rank test. We implemented Cox proportional hazards regression to estimate hazard ratios (HR) and 95 % confidence intervals (95 %CI) for freedom from distant metastasis (FFDM) and BCSS. Regression models were adjusted for age at diagnosis, tumor characteristics, and treatment variables that had an appreciable effect on the HR. Local–regional recurrence was defined from the date of diagnosis until the date of recurrence. Patients who had a prophylactic mastectomy after breast-conserving therapy were censored from the analysis at the date of surgery. FFDM was defined from the date of diagnosis to date of first distant metastasis. BCSS was determined from the date of diagnosis until death due to breast cancer. Overall survival was calculated from the date of diagnosis until death from any cause determined by the medical record or the Social Security death index.

Results

The study cohort consists of 264 women, including 89 *BRCA1* mutation carriers and 175 non-carriers. The median time to genetic testing was 4.9 months for carriers (1.4–16.4 months) and 4.2 months for non-carriers (1.5–9.4 months; $P = 0.31$). Clinical and tumor characteristics are presented in Table 1. Mutation carriers were significantly younger at diagnosis (median age 41.8 vs. 47.8 years; $P < 0.0001$). There were no significant differences in tumor characteristics including histologic type,

Table 1 Clinical and pathologic features at presentation

	BRCA1 carrier ($n = 89$)	Non-carrier ($n = 175$)	P
Age at diagnosis (years)—mean ± SD	41.8 ± 8.5	47.8 ± 10.9	<0.0001
Histology—*n* (%)			0.48
Ductal	86 (96.6)	164 (93.7)	
Lobular	2 (2.2)	0 (0.0)	
Mixed ductal/lobular	1 (1.1)	4 (2.3)	
Other	0 (0.0)	7 (4.0)[a]	
Tumor size (cm)—median (IQR)	1.8 (1.2–3.0)	2.0 (1.4–3.0)	0.15
Tumor grade—*n* (%)			1.0
1	0 (0.0)	1 (0.6)	
2	6 (6.7)	12 (6.9)	
3	83 (93.3)	162 (92.6)	
Lymphovascular invasion—*n* (%)			0.85
Present	36 (40.4)	72 (41.1)	
Absent	51 (57.3)	97 (55.4)	
Unknown	2 (2.2)	6 (3.4)	
Positive lymph nodes—*n* (%)			0.74
Present	38 (42.7)	71 (40.6)	
Absent	51 (57.3)	104 (59.4)	
T classification—*n* (%)			0.14
T1	55 (61.8)	90 (51.4)	
T2	29 (32.6)	60 (34.3)	
T3	2 (2.2)	15 (8.6)	
T4	2 (2.2)	9 (5.1)	
Unknown	1 (1.1)	1 (0.6)	
N classification—*n* (%)			0.48
N0	50 (56.2)	89 (50.9)	
N1	24 (27.0)	60 (34.3)	
N2	13 (14.6)	18 (10.3)	
N3	2 (2.2)	5 (2.9)	
Unknown	0 (0.0)	3 (1.7)	
Stage—*n* (%)			0.63
1	35 (39.3)	57 (32.6)	
2A	29 (32.6)	55 (31.4)	
2B	8 (9.0)	27 (15.4)	
3A	13 (14.6)	23 (13.1)	
3B	2 (2.2)	8 (4.6)	
3C	2 (2.2)	5 (2.9)	

SD standard deviation, *IQR* interquartile range

[a] Other histology includes adenoid cystic (1), metaplastic (2), carcinoma with squamoid features (1), and unknown (3)

size, grade, lymphovascular invasion (LVI), or the presence of positive lymph nodes between carriers and non-carriers (all $P > 0.15$). The most common histologic type was invasive ductal carcinoma among both carriers (96.6 %) and non-carriers (93.7 %). Carriers and non-carriers had similar rates of high histologic grade (93.3 and 92.6 %, respectively), LVI (40.4 and 41.1 %, respectively), and axillary lymph node involvement (42.7 and 40.6 %, respectively).

Table 2 Treatment for primary breast cancer

	BRCA1 carrier ($n = 89$)	Non-carrier ($n = 175$)	P
Surgery—*n* (%)			0.006
Partial mastectomy	38 (42.7)	106 (60.6)	
Mastectomy	51 (57.3)	69 (39.4)	
Chemotherapy—*n* (%)			0.31
Anthracycline-based (AC,CAF)	26 (29.2)	45 (25.7)	
Anthracycline and taxane-based (AC + T)	53 (59.6)	106 (60.6)	
Platinum and anthracycline-based (AC)	0 (0.0)	8 (4.6)	
Taxane-based (TC)	4 (4.5)	9 (5.1)	
CMF	6 (6.7)	5 (2.9)	
Other	0 (0.0)	2 (1.2)	
Radiation—*n* (%)			0.0006
Yes	51 (57.3)	136 (77.7)	
No	38 (42.7)	39 (22.3)	
Bilateral salpingo-oophorectomy—*n* (%)			<0.0001
Yes	69 (77.5)	10 (5.7)	
No	20 (22.5)	165 (94.3)	
Prophylactic mastectomy—*n* (%)			<0.0001
Yes	49 (55.1)	15 (8.6)	
No	38 (42.7)	160 (91.4)	
Unknown	2 (2.2)	0 (0.0)	

CMF cyclophosphamide, methotrexate and fluorouracil, *IQR* interquartile range

Treatment characteristics are shown in Table 2. The type of chemotherapy used was similar between the carriers and non-carriers ($P = 0.31$), with approximately 90 % in each group receiving an anthracycline plus alkylator and 60 % receiving an anthracycline, alkylator, and taxane. However, carriers were less likely to have undergone breast-conserving therapy ($P = 0.006$) or receive radiation ($P = 0.0006$). With regard to prophylactic surgery, 77.5 % of carriers underwent bilateral salpingo-oophorectomy (BSO) and 55.1 % underwent prophylactic mastectomy compared with 5.7 and 8.6 % of non-carriers, respectively (both $P = <0.0001$). The date of surgery was available for 76 of the 79 women who underwent BSO; 86.8 % of

Table 3 Timing of bilateral salpingo-oophorectomy (BSO)

	BRCA1 carrier ($n = 68$)	Non-carrier ($n = 8$)	P
Age at BSO (years)—median (IQR)	42.7 (39.2–47.1)	55.1 (45.6–58.1)	0.01
BSO after diagnosis—n (%)	59 (86.8 %)	6 (75.0 %)	
Time to BSO (mos)—median (IQR)	12.7 (9.6–28.8)	45.0 (18.6–70.7)	0.04
BSO before diagnosis—n (%)	9 (13.2 %)	2 (25.0 %)	
Time to diagnosis (mos)—median (IQR)	−29.5 (−122.3 to −19.5)	−44.8 (−62.9 to −26.7)	1.0

Date of BSO missing for three women

IQR interquartile range

Table 4 Recurrence and secondary cancer

	BRCA1 carrier ($n = 89$)	Non-carrier ($n = 175$)	P
Local recurrence			0.44
After breast-conserving therapy	3 (3.4)	12 (6.9)	
After mastectomy	6 (6.7)	8 (4.6)	
No local recurrence	80 (89.9)	155 (88.6)	
Site of local recurrence			
Chest wall/scar	3 (33.3)	12 (60.0)	0.25
Ipsilateral breast	2 (22.2)	6 (30.0)	1.0
Lymph node	4 (44.4)	2 (10.0)	0.06
Distant metastasis			0.88
Yes	19 (21.4)	40 (22.9)	
No	70 (78.7)	135 (77.1)	
First site(s) of distant metastasis[a]			
Lung	7 (36.8)	18 (45.0)	0.55
Bone	4 (21.1)	12 (30.0)	0.55
Brain	3 (15.8)	2 (5.0)	0.32
Liver	4 (21.1)	11 (27.5)	0.75
Other nodal groups	2 (10.5)	6 (15.0)	1.0
Other sites	3 (15.8)	4 (10.0)	0.67
All sites of distant metastasis[a]			
Lung	9 (47.4)	20 (50.0)	0.85
Bone	6 (31.6)	15 (37.5)	0.66
Brain	7 (36.8)	11 (27.5)	0.47
Liver	6 (31.6)	15 (37.5)	0.66
Other nodal groups	5 (26.3)	10 (25.0)	1.0
Other sites[b]	3 (15.8)	7 (17.5)	1.0
Second breast cancer			0.005
Yes	11 (12.4)	6 (3.4)	
No	78 (87.6)	169 (96.6)	

[a] Some women had more than one site of distance metastasis

[b] Other sites for *BRCA1* carriers include abdominal wall (1), and contralateral breast (1) and adrenal (1). Other sites for noncarriers include peritoneum (1), skin (2), pleura (3), and abdominal wall (1)

carriers and 75.0 % of non-carriers underwent BSO after their breast cancer diagnosis with the time to BSO significantly shorter in *BRCA1* carriers (median, 12.7 and 45.0 months, respectively; $P = 0.04$). Among *BRCA1* carriers who underwent BSO after breast cancer diagnosis, 71.2 % had the BSO within 2 years and 93.2 % within 5 years of diagnosis. The 68 carriers who underwent BSO had a significantly younger median age at surgery (42.7 years) than the eight non-carriers at the time of their BSO (55.1 years; $P = 0.01$; Table 3). Only eight mutation carriers underwent BSO after age 50.

The median follow-up time was similar for carriers (59.6 months; range, 6.6–175.9 months) and non-carriers (53.2 months; range 5.7–153.3 months; $P = 0.49$). Table 4 shows patterns of recurrence in both groups. The incidence of local–regional recurrence was not significantly different between carriers (10.1 %) and non-carriers (11.4 %; $P = 0.75$). Carriers were more likely (12.4 %) than non-carriers (3.4 %) to develop a second primary breast cancer ($P = 0.005$).

As shown in Table 4, the most common site of first distant metastasis for both mutation carriers and non-carriers was lung (36.8 and 45.0 %, respectively), followed by liver (21.1 and 27.5 %, respectively) and bone (21.1 and 30.0 %, respectively). The brain was the first site of metastatic disease in 15.8 % of carriers and 5.0 % of non-carriers ($P = 0.32$). A similar pattern was seen when comparing the frequency of brain metastases at any time ($P = 0.47$).

The lack of difference in incidence of distant metastatic disease between *BRCA1* carriers and non-carriers is reflected in the FFDM curves (Fig. 1) and the crude HR of 0.90 (95 % CI 0.52–1.6; Table 5). At year five, FFDM was 80.5 % for *BRCA1* mutation carriers and 76.9 % for non-carriers. Of the potential confounders considered, only BSO, prophylactic mastectomy, and LVI appreciably altered the HR for *BRCA1* mutation carrier status in the final model. When adjusting for these confounders and age, the HR for FFDM was 1.6 (95 % CI 0.69–3.8) for carriers compared to non-carriers.

There were 42 deaths, all attributed to breast cancer: ten (11.2 %) occurred in carriers and 32 (18.3 %; $P = 0.14$) in non-carriers; the median time to death was 36.6 months (23.3–50.4) and 26.4 months (22.8–37.5; $P = 0.37$), respectively. At 5 years BCSS was 88.1 % for *BRCA1* carriers and 81.4 % for non-carriers, with a crude HR of 0.60 (95 % CI 0.29–1.2; Table 5; Fig. 2). After adjusting for BSO, prophylactic mastectomy and age, the HR was 2.1

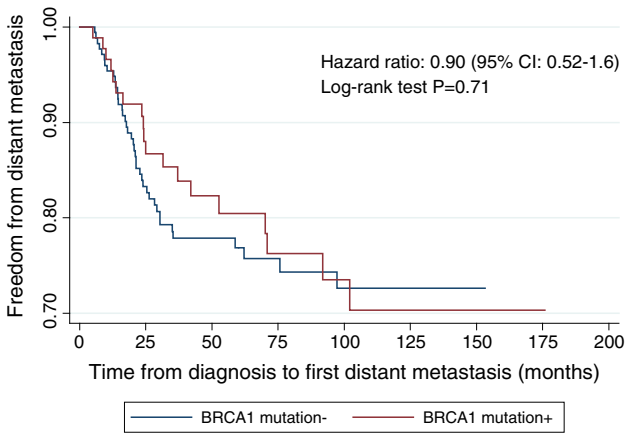

Fig. 1 Freedom from distant metastasis (FFDM) by *BRCA1* mutation status

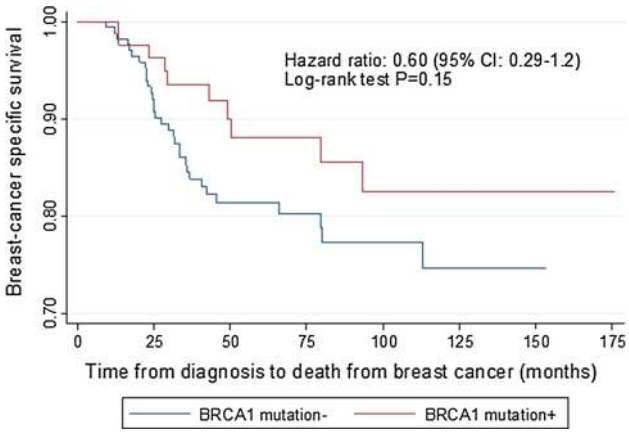

Fig. 2 Breast cancer-specific survival (BCSS) by *BRCA1* mutation status

(95 % CI 0.80–5.5). *BRCA1* carriers who underwent a BSO had a significantly lower rate of death from TNBC, with an adjusted HR of 0.30 (95 % CI 0.10–0.94).

Discussion

We found no differences in the likelihood of developing distant metastatic disease or in breast cancer survival among women with TNBC who received anthracycline and alkylator-based chemotherapy according to *BRCA1* status. This is consistent with our earlier findings as well as those by Bayraktar et al. [7, 8]. This is also consistent with the finding by Arun et al. [9] that pathologic complete response (pCR) was similar in 33 *BRCA1* carriers and 42 non-carriers with TNBC receiving anthracycline and taxane-based neoadjuvant chemotherapy.

One possible explanation for the lack of difference in long-term outcomes between carriers and non-carriers is that a significant proportion of sporadic TNBC share many biologic similarities with *BRCA1*-associated TNBC. *BRCA1*-related breast cancers and the majority of sporadic TNBC cluster within the basal subgroup by gene expression profiling and express basal cytokeratins and EGFR [10, 11]. Some sporadic basal-like breast cancers may also have a dysfunctional *BRCA1* pathway due to gene promoter methylation or transcriptional inactivation [12, 13].

A second possible explanation for the lack of difference in outcomes observed is that anthracycline-based chemotherapy fails to exploit biologic differences that do exist

Table 5 Univariable regression for freedom from distant metastasis and breast cancer-specific survival

	Freedom from distant metastasis crude HR (95 % CI)	*P*	Breast cancer-specific survival crude HR (95 % CI)	*P*
Participant characteristics				
BRCA mutation carrier	0.90 (0.52–1.6)	0.71	0.60 (0.29–1.2)	0.16
Age per 10 years	0.98 (0.77–1.2)	0.83	1.1 (0.80–1.4)	0.69
Tumor characteristics				
Tumor size per 10 cm	1.2 (1.0–1.4)	0.02	1.2 (1.1–1.5)	0.008
Lymphovascular invasion	3.5 (2.0–6.1)	<0.0001	3.9 (2.0–7.6)	<0.0001
Positive lymph node	3.3 (1.9–5.6)	<0.0001	3.6 (1.9–6.9)	0.0001
T stage	2.0 (1.6–2.7)	<0.0001	1.9 (1.4–2.5)	0.0001
N stage	3.0 (2.2–4.1)	<0.0001	3.1 (2.2–4.5)	<0.0001
AJCC stage	3.4 (2.3–5.0)	<0.0001	3.3 (2.1–5.2)	<0.0001
Treatment characteristics				
Bilateral salpingo-oophorectomy	0.54 (0.28–1.0)	0.05	0.35 (0.15–0.83)	0.02
Radiation	2.2 (1.1–4.5)	0.03	2.8 (1.1–7.2)	0.03
Mastectomy[a]	1.8 (1.1–3.0)	0.03	1.4 (0.78–2.6)	0.25
Prophylactic mastectomy	0.55 (0.27–1.1)	0.10	0.25 (0.08–0.81)	0.02

T stage, N stage, and AJCC stage are modeled as continuous variables

HR hazard ratio, *CI* confidence interval, *AJCC* American Joint Committee on Cancer

[a] Reference group is women who had a partial mastectomy

between BRCA-associated and sporadic TNBC. BRCA1 functions in the FA-BRCA pathway of double-strand DNA damage repair and BRCA-associated breast cancers therefore have defects in homologous recombination. TNBC has been shown to be a heterogeneous disease by gene expression profiles with at least six distinct biologic subtypes [14, 15]. The basal-like (BL1, BL2) subtypes have higher expression of DNA damage response genes, preferentially respond to platinum in vitro and are potentially most akin to *BRCA1*-associated breast cancers, but represent only a subset of sporadic TNBC [14]. Consistent with this hypothesis, Mulligan et al. [16] found that 55 % of unselected TNBC had a defect in the FA-BRCA pathway measured by a 44 gene microarray assay.

Therefore, it is possible that BRCA1 deficient breast cancers would be more sensitive than sporadic breast cancers to double-strand DNA damaging agents such as platinum or poly-(ADP) ribose polymerase (PARP-1) inhibitors. Three neodjuvant studies recently reported pCR rates approximately 15–25 % higher in unselected TNBC with the addition of carboplatin to anthracyclines and taxanes [17–19]. Response rates according to *BRCA* mutation have not yet been reported for these trials. In a single arm phase II study using a platinum-based neoadjuvant regimen that did not include anthracyclines or taxanes, Telli et al. [20] reported a 33 % pCR in 61 patients with sporadic TNBC and a 56 % pCR in 16 patients with BRCA-associated TNBC. Higher pCR rates were achieved in those sporadic TNBC assessed to have a higher homologous recombination defect (HRD), measured by loss of heterozygosity of intermediate size chromosomal areas [20]. Likewise, using cisplatin alone Silver et al. demonstrated a pCR in 15 % of 26 patients with sporadic TNBC and in both patients with *BRCA1*-associated TNBC; pCR was significantly higher in those TNBC with low BRCA1 mRNA expression. Indeed pCR rates greater than 70 % have been reported with cisplatin alone in *BRCA1*-associated breast cancer [21, 22]. While these pCR rates are higher than those reported in both *BRCA1*-associated breast cancers treated with anthracycline-based chemotherapy and in sporadic TNBC treated with cisplatin monotherapy, direct comparison between studies involving small numbers of cases is problematic. [9, 21, 23] A randomized trial comparing neoadjuvant cisplatin and an anthracycline-based regimen in *BRCA1* mutation carriers with breast cancer is ongoing [24].

Also arguing against "BRCA-ness" in the majority of sporadic TNBC is that significant responses to PARP-1 inhibitor monotherapy have been demonstrated in germline BRCA-deficient but not in sporadic TNBC. [25, 26] In BRCA1-deficient cancers, the effectiveness of PARP inhibitors is thought to be due to synthetic lethality as a result of the defect in homologous recombination.

We also found no difference in the sites of disease recurrence including the brain between *BRCA1* carriers and non-carriers with TNBC. To our knowledge, only one other group has examined whether *BRCA1* carriers with breast cancer have a higher likelihood of brain metastases. Albiges et al. [27] found that among patients with metastases, brain metastases were more frequent in *BRCA1* carriers compared to BRCA2 carriers and non-carriers. However, in their series 75 % of breast cancers in BRCA2 carriers and 79 % in non-carriers were ER-positive in contrast to 35 % in *BRCA1* carriers. TNBC is associated with a higher incidence of brain metastases than ER+ HER2-negative breast cancer. Several case reports and small series have suggested an increased incidence of brain metastases in ovarian cancer patients with either inherited *BRCA1* or BRCA2 (*BRCA1*/2) mutations or somatic tumor loss of *BRCA1*/2 [28–31]. It is not clear whether this finding, if real, reflects longer survival in ovarian cancer patients with a *BRCA1/2* mutation or an intrinsic biologic difference in their cancers.

In our analysis *BRCA1* carriers who underwent a BSO had a significantly lower rate of death from TNBC, with an adjusted HR of 0.30 (95 %CI 0.10–0.94). This benefit cannot be explained by a decrease in second breast cancers, since none of the 18 women who developed a second breast cancer died during the study period and only one developed metastatic disease. Previous reports have suggested improved breast cancer survival in *BRCA1* carriers who undergo oophorectomy [8, 32]. For oophorectomy to influence recurrence and survival from TNBC one might expect that BSO would occur either before diagnosis or within 5 years after diagnosis when almost all TNBC recurrences occur. [33, 34] In the current study, 86.8 % of mutation carriers who underwent BSO did so after their breast cancer diagnosis and relatively soon after diagnosis: 71.2 % had the BSO within 2 years and 93.2 % within 5 years. Whether the effect of BSO is related to a hormone-mediated mechanism cannot be assessed in this study since only eight mutation carriers underwent BSO after age 50. In addition, there were insufficient numbers of non-carriers who underwent oophorectomy to assess any possible effect on BCSS. The benefit of oophorectomy in patients with TNBC needs to be further examined in other, preferably prospective studies that include both *BRCA1/2* carriers and non-carriers.

Outcomes may be affected in cohort studies by survivorship bias as the timing of genetic testing may select for long-term survivors. A strength of this study is that all 264 patients had genetic testing within 36 months of diagnosis. Limitations of this study include the relatively small sample size and retrospective nature of the study which may introduce bias due to unmeasured confounders and patient selection. In addition, all patients were treated at

two academic hospitals which could potentially limit the generalizability of the findings.

In summary, this study found no difference in the clinical outcomes of *BRCA1* mutation carriers compared to non-carriers with TNBC who received anthracycline and alkylator-based chemotherapy in the adjuvant setting. These findings may support the discovery that many sporadic TNBC share significant biologic similarities with *BRCA1*-related TNBC. Alternatively, alkylating and anthracycline-based chemotherapy may not exploit any biologic differences that exist between *BRCA1*-related and sporadic TNBCs including defects in double-strand DNA break repair. We also did not find any difference in sites of TNBC metastatic relapse, including brain metastases, between carriers and non-carriers. We found that oophorectomy substantially increased freedom from distant recurrence and breast cancer-related survival in *BRCA1* carriers with TNBC. This finding needs to be confirmed and should be explored in those with sporadic TNBC as well.

Conflict of interest The authors declare that they have no conflict of interest.

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Ethical Standards All research activities carried out for this study comply with the current laws of the United States of America, where this research took place.

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